OPTOMETRISTS AND DISPENSING OPTICIANS BOARD

Te Poari o ngā Kaimātai Whatu me ngā Kaiwahakarato Mōhiti

Oral Medication Guidelines – Blepharitis

Description

Blepharitis can be classified according to the anatomic location, with anterior blepharitis affecting the eyelid skin, base of the eyelashes and the lash follicles. Anterior blepharitis can be staphylococcal, seborrheic, demodectic or mixed. The staphylococcal form is thought to result from an abnormal cell-mediated response to *Staphylococcus aureus* cell wall components, and is more common and severe in patients with atopic dermatitis. Seborrheic blepharitis is associated with seborrheic dermatitis involving the scalp, nasolabial folds, and the skin behind the ears (Bowling, 2016).

Demodex mites, *Demodex folliculorum* and *Demodex brevis,* are common ectoparasites, found on the skin. The mites inhabit follicles with or without hair, and they have a predilection for areas with a high production of sebum (Wesolowska *et.al.,* 2014). *Demodex folliculorum* are found predominantly in the lash follicles, while *Demodex brevis* burrow into sebaceous and meibomian glands. When they inhabit eyelash follicles in high numbers, Demodex mites can cause or exacerbate chronic anterior blepharitis. Demodex can cause physical damage to the lid margin, and carry bacteria, which release antigenic exotoxins, on their surface. In addition, the proteins inside the mites, and their products, are thought to trigger inflammatory responses, resulting in Demodex blepharoconjunctivitis (Wolffsohn *et.al.,* 2017).

Meibomian gland dysfunction (MGD) is the most common form of posterior blepharitis. It is characterised by a chronic, diffuse abnormality of the meibomian glands resulting in duct obstruction and changes in glandular secretion (Nichols *et.al,* 2011). Patients with early or mild MGD may be asymptomatic and do not meet the criteria for dry eye disease. As the condition progresses patients are likely to become more symptomatic, reporting symptoms consistent with dry eye disease, and more pronounced changes to the posterior lid margin occur.

Significance

Chronic blepharitis is a common cause of ocular discomfort and irritation and can adversely affect quality of life in affected individuals. It is not uncommon for anterior and posterior blepharitis to co-exist.

Prevalence

MGD is the leading cause of dry eye disease (Nichols *et.al.,* 2011), and up to 40 to 50% of patients seen in optometric practice show signs and/or symptoms of MGD (Lemp *et.al.,* 2009, Xue *et. al.*, 2017). Anterior blepharitis is a common ocular disorder, frequently encountered by optometrists in clinical practice, with approximately 15% of patients presenting with specific symptoms (Lemp *et.al.,* 2009, Xue *et al.*, 2017).

Demodex infestation increases with age: 84% of the population aged 60, and 100% aged over 70 years exhibit Demodex infestation (Wolffsohn *et.al.,* 2014). Demodex can spread from the body to the face and eyelids, causing anterior blepharitis and ocular surface disease. Approximately 30% of patients with chronic blepharitis have Demodex infestation, however the prevalence is not dissimilar in those without blepharitis (Kemal *et.al.,* 2005).

Signs and symptoms

Typical symptoms of blepharitis can include (Bowling, 2016):

- burning/stinging sensation
- grittiness
- photophobia
- crusting and redness of the lid margins
- poor contact lens tolerance.

Signs of blepharitis can include (Bowling, 2016):

- deposits (crusting/scales) around the lashes
- trichiasis
- ulceration, telangiectasia and notching of the lid margin
- madarosis
- abnormal meibomian gland secretions and capped gland orifices
- meibomian gland loss on lid transillumination
- foaming of the tear film
- corneal and conjunctival staining
- mild papillary conjunctivitis and hyperaemia
- corneal vascularization and infiltrates
- occasionally, live Demodex will be observable with high magnification (x40) slit lamp biomicroscopy. Cylindrical dandruff or sleeves are considered pathognomonic of ocular Demodex infestation (Gao *et.al.,* 2005).

There is often poor correlation between signs and symptoms, making it difficult to objectively assess treatment benefit.

Clinical evaluation

The following sequence of tests has been recommended for the evaluation of patients with ocular surface disease (Nichols *et.al.,* 2011; and Wolffsohn *et.al.,* 2017):

1. Administration of a validated dry eye questionnaire, e.g. the Ocular Surface Disease Index[1] (Schiffman *et.al.,* 2000), or the DEQ5 Questionnaire (Wolffsohn *et.al.,* 2017).
2. Calculation of blink rate and blink interval.
3. Measurement of tear meniscus height.
4. Non-invasive break-up time (NIBUT), whenever possible (Wolffsohn *et.al.,* 2017).
5. Measurement of tear osmolarity, if available.
6. Tear break-up time (TBUT) with minimal fluorescein (only if NIBUT not possible) (Wolffsohn *et.al.,* 2017).
7. Grading of conjunctival and corneal staining with fluorescein and/or lissamine green, including staining of the lid wiper area.
8. Schirmer or Phenol Red Thread test.
9. Eyelid and MGD assessment – quantification of morphological lid and lash features, meibomian gland expressibility and quality of meibum, and meibography to grade or quantify meibomian gland drop out (Nichols *et.al.,* 2005).

The TFOS DEWS II diagnostic criteria state that an OSDI symptom score of ≥ 13 or a DEQ-5 score of ≥ 6 plus one or more positive sign of loss of tear film homeostasis (indicated by a non-invasive tear break up time < 10 seconds, osmolarity ≥ 308 mOsm/L in either eye or an inter-ocular difference of > 8 mOSm/L, or corneal (> 5 spots), conjunctival staining (> 9 spots) or lid wiper epitheliopathy (> 2 mm in length and > 25% of lid margin width)) signifies a positive diagnosis for dry eye disease (Craig, *et.al.,* 2017).

Differential diagnosis

1. **Anterior blepharitis** – noting possible signs of Demodex infestation
2. **Posterior blepharitis** – noting possible underlying causes, most commonly MGD, but also including infection, allergy or systemic conditions such as acne rosacea (Nelson *et.al.,* 2005)
3. **Aqueous deficient dry eye**
4. **Conjunctivitis** (allergic, viral or bacterial)
5. **Floppy eyelid syndrome**.

Management

1. **Patient recommendations and over-the-counter management**
    a. **Lid cleansing**: Lid hygiene is essential in the management of anterior blepharitis and helps to remove lid crusting. Traditional recommendations of cleansing with a mild dilution of baby shampoo, applied to the eyelids with a cotton bud or swab (Jones *et.al.,* 2017), have

[1] Available at: http://dryeyezone.com/documents/osdi.pdf

lost favour compared with commercially available, dedicated lid cleansers which are more effective, do not cause ocular surface damage and are better tolerated (Sung *et.al.,* 2018).

Tea tree oil is available in pre-formulated lid wipes and cleansers (e.g., Blephadex) that can be used daily for the management of Demodex (see below for rationale).

b. **Warm compresses:** Regular heat application is beneficial for MGD and to soften crusts at the base of the lashes. The recommended heat regimen is ten minutes twice a day, maintaining a temperature of 40°C (Jones *et.al.,* 2017). On-going application is required, and the optometrist needs to provide appropriate information and discuss the importance of compliance with their patients.

c. **Diet**: Increase in intake of omega-3 fatty acids has been shown to have anti-inflammatory properties and may help to improve the signs and symptoms of dry eye disease (Rashid *et.al.,* 2008). However, practitioners should caution patients against ingesting excessive doses of omega-3 fatty acids due to the possible anticoagulation effects.

d. **Environment control**: Improving ambient humidity, reducing draughts, and optimizing workstations.

e. **Tear supplementation**: Often MGD and aqueous-deficient dry eye co-exist, and supplementation with artificial tears may reduce tear film hyperosmolarity and risk of epithelial damage. The frequent use of artificial tears may also dilute toxins and pro-inflammatory mediators found in tears. To address the evaporative component of dry eye disease associated with MGD, tear supplementation that increases the lipid layer, e.g., lipid-containing drops or liposomal sprays, should be considered (Craig, J.P. *et. al.*, 2021).

f. **Manuka honey drops / gel**: Topical application of Manuka honey eye drops can reduce lid margin bacterial load (Albietz & Lenton, 2006). These are currently available in New Zealand as Optimel™ eye drops and eye gel, containing *Leptospermum sp.* (Manuka) honey 165 mg/g and 980 mg/g respectively. In combination with conventional therapy (hot compresses, lid massage and preservative free lubricant), 16% drops and 98% Manuka gel have been shown to be an effective adjunctive therapy in the treatment of MGD (Albietz & Lenton, 2006).

2. In-office management

a. **Intense pulsed light (IPL) therapy**: Application of IPL (broad spectrum light of wavelength between 580 and 1200 nm) has demonstrated benefits in MGD by improving meibomian gland function. Improvements in lipid layer thickness, tear film stability and symptoms have been demonstrated in a randomised, double-masked clinical trial (Craig *et.al.,*

2015). Melanin preferentially absorbs the emitted energy placing darker skins at higher risk of burning, therefore modifying the fluence (power) level according to skin pigmentation is essential. Tightly fitting metal goggles are necessary to protect the globe from the emitted light.

b. **Tea Tree oil**: Tea Tree oil is an essential oil from the Paperbark or Tea Tree. The oil exhibits antimicrobial, antifungal, antiviral and anti-inflammatory properties, and is toxic to Demodex. However, tea tree oil can be toxic to the ocular surface and causes stinging and irritation if used in its pure form. An in-office treatment of 50% tea tree oil to the lid margin is effective in resolving the symptoms and lid margin inflammation associated with Demodex blepharitis (Cheng *et.al.,* 2015). This in-office treatment can be complemented with the daily use of lid hygiene measures as described above.

c. **Therapeutic gland expression**: This involves physical meibomian gland expression for therapeutic benefit. It is not to be confused with diagnostic expression, where minimal force is used to determine whether the gland is functional. Therapeutic meibomian gland expression has been shown to be an effective treatment for MGD (Korb & Greiner, 1994). It can be performed with a Mastrota paddle, with the paddle placed on the lower lid palpebral conjunctiva while the clinician's thumb applies pressure to the outer lid surface overlying the paddle (Korb & Blackie, 2011). However, it should be noted that this forceful expression of the glands can be very uncomfortable for some patients, with one study demonstrating that only 16 of 28 patients were able to tolerate the force required for partial therapeutic expression (Korb & Blackie, 2011). This is best performed after heating of the glands via warm compresses, latent heat application (e.g. Blephasteam®) or IPL application.

d. **Thermal pulsation (**e.g. LipiFlow®**):** This involves heating the meibomian glands via the palpebral conjunctiva of the inner eyelid surface to 42.5 °C during a single, bilateral, 12 minute, in-office procedure. The LipiFlow® treatment has been shown to be safe and effective for the sustained treatment of MGD, some effects of which may persist for months or years (Greiner, 2013; 2016). A three-month prospective, randomized, cross-over, observer-masked clinical trial comparing LipiFlow® to twice daily hot compresses, lid massage and lid hygiene, showed that a single LipiFlow® treatment was at least as effective as the daily routine, and the effects were sustained for 6 months (Finis *et.al.,* 2014). Hand-held thermal pulsation devices (e.g. iLux®) are becoming more commonly available across the world but are not yet commercially available in New Zealand.

e. **Intraductal meibomian gland probing**: This involves penetrating the meibomian gland orifice, perpendicular to the lid margin, with a 2 mm probe, under local anaesthesia (Maskin, 2010). The aim of this treatment is to mechanically open the meibomian gland orifice and overcome ductal stenosis, to improve MGD symptoms. Orifice haemorrhage

is frequently noted during the procedure (Maskin, 2010). As haemorrhage is indicative of epithelial breach, and is therefore a restricted task, meibomian gland probing is beyond the scope of optometric practice in New Zealand.

f. **Amniotic membrane:** In cases of severe dry eye disease, for example, in patients with Stevens Johnson syndrome or ocular cicatricial pemphigoid, amniotic membrane grafts may be considered if there are persistent epithelial defects or ulceration (Jones *et.al,* 2017). Patients with these conditions will usually be under the care of a corneal specialist ophthalmologist. Please refer to the ODOB position statement on amniotic membrane.

3. Topical pharmacological treatment

a. **Topical antibiotics**: May be useful in decreasing the bacterial load on the eyelids. Topical azithromycin 1% eye drops (twice daily) have been shown to be particularly effective and significantly improve meibomian gland plugging, meibomian gland secretions and eyelid hyperaemia, in addition to patient symptoms (Luchs, 2008), however, topical azithromycin is not currently available in NZ. The long-term use of topical antibiotics to reduce the lid margin bacterial load in anterior blepharitis is not routinely recommended. A Canadian consensus advocated the short-term use of topical antibiotics (e.g., Fusidic acid 1%, twice daily) (Jackson, 2009).

b. **Topical corticosteroids**: Inflammation may be present or absent in MGD and therefore, the use of steroid eye drops is not necessarily beneficial. Furthermore, use of steroids is questionable when there is the potential of sight-threatening complications in a disease entity that is non-sight threatening (Geerling *et. al.,* 2011). Where deemed necessary in a flare-up, topical steroid use should be prescribed for a restricted period (e.g., 2 weeks), and should be limited as much as possible to low penetration steroids (e.g. fluorometholone 0.1%). These steroids have reduced risk of corticosteroid-related adverse effects, including increased intraocular pressure, and posterior subcapsular cataract (McGhee *et.al.,* 2002).

c. **Topical cyclosporin:** Although this steroid-sparing medication is indicated primarily for aqueous deficient dry eye disease, there may be some role in treating MGD, for example when aqueous deficiency and evaporative dry eye co-exist, but the evidence for success in MGD management is equivocal. In one small study of 33 patients, topical cyclosporin did not improve symptoms, but did decrease the number of blocked meibomian glands (Perry *et.al.,* 2006). Cyclosporin eye drops can be prepared by a compounding pharmacy (cyclosporin 0.05%) or prescribed as Restasis under Section 29 of the Medicines Act 1981 (medical practitioners only). For more information about Section 29 medications, consult the Medsafe website. Prescribing of compounded cyclosporin 0.05% eye drops is not restricted to medical practitioners, however, it is not subsidised. With a superior safety profile relative to corticosteroids, topical cyclosporin is typically reserved for treating

severe ocular surface disease where long-term anti-inflammatory therapy is indicated, and in most cases, will be initiated by an ophthalmologist.

d. **Tacrolimus ointment**: Also known as FK506, tacrolimus is a calcineurin inhibitor with potent immunosuppressive properties (Hooks, 1994). Tacrolimus has a similar mechanism of action to cyclosporine; it blocks IL-2 production, thereby inhibiting further T-lymphocyte proliferation (Hooks, 1994). Prepared as an ointment, this drug demonstrates good penetration through corneal and conjunctival tissue and effective reduction in clinical signs of inflammation for patients with atopic blepharokeratoconjunctivitis (Hooks, 1994). Tacrolimus is therefore gaining interest as a therapy to control ocular surface inflammatory disease.

   Topical tacrolimus (available as compounded ophthalmic ointment or eye drops) is available on prescription by authorised prescribers, however it is not subsidised. As this medication is used to treat severe ocular surface conditions that have not responded to conventional treatments, topical tacrolimus is generally prescribed by ophthalmologists. Most published studies detail efficacy in chronic atopic blepharoconjunctivitis, however, tacrolimus 0.03% ointment has also been used in the treatment of refractory blepharitis (Sakasssegawa-Waves *et.al.,* 2017). A small amount of ointment (approximately 0.5 cm) is applied to the eyelid margin and eyelashes, or instilled into the lower conjunctival fornix, once or twice daily (Shoghy, 2017). Treatment duration varies but is generally 14 to 30 days (Sakasssegawa-Waves *et.al.,* 2017).

   Tacrolimus ointment is generally well tolerated and safe, and adverse effects are usually minor (transient ocular surface irritation in approximately 50% of patients (Erdinest & Soloman, 2014)). Serious adverse effects are rare. However, a recent European multicentre study (Castellsague *et.al,* 2018) found an increase in the incidence of lymphoma in children (and adults, to a lesser extent) treated with topical tacrolimus, with risk increasing with higher cumulative dose. There were weaker associations for melanoma and non-melanoma skin cancer.

4. Oral pharmacological treatment:

a. **Tetracyclines e.g. doxycycline, minocycline and tetracycline**: Can be used to treat a number of ocular surface diseases including ocular rosacea, blepharitis, recurrent corneal erosion and dry eye disease. Tetracyclines decrease the secretion of bacterial lipases that break down the normal meibum lipids into free fatty acid fragments. They also have anti-collagenase and anti-matrix metalloproteinase (MMP) properties, which reduce the inflammatory effects of MGD. Although the mechanisms of action are not fully understood, tetracyclines appear to improve the lipid profile of the tear film in patients with MGD.

The recommended dosage of doxycycline and minocycline for anti-inflammatory treatment of MGD is 50mg to 100mg once daily, for 3 months (i.e., much lower daily dose than the therapeutic antibiotic dose, Geerling *et.al.,* 2011) Tetracyclines should always be administered with food or adequate amounts of fluid and the patient should remain sitting or standing for up to 2 hours after administration to minimise oesophageal irritation.

Tetracyclines should not be administered to patients taking warfarin as the interaction may enhance warfarin's blood-thinning properties. Tetracyclines are also contraindicated during pregnancy and childhood (up to 12 years of age) as they affect tooth development and can lead to permanent discolouration of the teeth. They can also interfere with bone development, although in neonates this appears to be reversible when tetracyclines are discontinued. Tetracyclines can cross the placenta and have been found in the breast milk of lactating women, and therefore should not be used during pregnancy or while breast-feeding.

Gastrointestinal side effects are common, particularly with higher doses of tetracyclines, and these include nausea, dyspepsia, diarrhoea, and anorexia. Photosensitivity can occur in some individuals and treatment should be discontinued at the first sign of skin erythema. Patients should be warned to apply adequate sunscreen and to cover up to ensure protection. Less common adverse reactions include rashes, dermatitis, benign intracranial hypertension, and haematological abnormalities. Minocycline is generally used less frequently due to its comparatively higher rate of side effects, including drug-induced lupus (Shapiro *et.al.,* 1997).

b. **Macrolides:** These medications (e.g., azithromycin) have anti-inflammatory and anti-MMP properties, and azithromycin has been shown to have some success in treating patients with MGD by altering the lipid properties of meibomian gland secretions (Foulk *et.al.,* 2010).

Current oral azithromycin prescribing protocols for posterior blepharitis vary, and there is not universal consensus. One recommended regimen is 500 mg on day one with 250 mg per day for the following four days (a 5-day course). This has been shown to have a similar effect, on improving patient symptoms and clinical signs, as a one-month course of doxycycline (200 mg per day, Kashkouli *et.al.,* 2015). Alternatively, a pulsed dosage has been suggested, with oral azithromycin prescribed at 500 mg per day for 3 days in three cycles, with an interval of 7 days between each cycle (Igami *et.al.,* 2011).

Oral erythromycin has demonstrated efficacy in children with ocular rosacea (Nazir *et.al.,* 2004) and blepharokeratitis (Meisler *et.al.,* 2000), and may be considered an alternative

therapy option for patients where other oral medications are contraindicated or poorly tolerated. In children, the recommended dose is 250 mg four times daily, although adult doses have not been established (Meisler *et.al.,* 2000).

Macrolides are contraindicated in patients with known hypersensitivity, and patients with severely impaired hepatic function. Erythromycin has been reported to aggravate muscle weakness associated with myasthenia gravis. It should not be used in patients who are taking theophylline due to the potential of theophylline toxicity and reduced efficacy of erythromycin. Erythromycin should also not be combined with anti-coagulant agents or benzodiazepines.

The most common side effects of macrolides are gastrointestinal upset including nausea, diarrhoea, vomiting and abdominal pain. Azithromycin use has been linked to ventricular arrhythmias associated with prolonged QT interval, and this should be considered when balancing risks versus benefits. There have also been isolated reports of central nervous system disturbance including confusion, hallucinations, tinnitus, seizures and vertigo following macrolide use.

c. **Ivermectin**: An anti-parasitic agent with anti-inflammatory activity (Kircik *et.al.,* 2016). It has long been used to treat parasitic infections in mammals. More recently, ivermectin has been used 'off-label' to treat blepharitis associated with Demodex. Ivermectin has a high affinity for peripheral nervous system glutamate-gated chloride ion channels in invertebrates, resulting in increased cell-membrane permeability to chloride ions, leading to parasite paralysis and death (Salem *et. al.,* 2013). Ivermectin has been shown to reduce the number of Demodex mites found in the lashes of patients with chronic Demodex-associated blepharitis (Filho *et.al*., 2011; & Holzchuh *et.al.,* 2011).

In New Zealand, Ivermectin is available as Stromectol® 3 mg tablets. In two published studies, patients received two doses, one week apart, of 200 µg per kg of body weight (Salem *et.al.,* 2013) (Holzchuh *et.al.,* 2011). For an individual weighing 70 kg, this is 14.2 milligrams (close to five 3 mg tablets). Another study simplified the dose, by administering 6 mg twice a day for one day, followed by another dose 14 days later (Filho *et.al*., 2011).

Side effects of oral ivermectin are usually minor. They can include flushing, nausea, light-headedness, diarrhoea, headache, joint pain, and transient tachycardia (Holzchuch *et.al.,* 2011). Ivermectin is primarily metabolized by the liver, and there is minimal clearance by the kidneys. It does not require dose-adjustment for individuals with renal failure. There have been some reports of a mild anticoagulation effect, but this is not usually significant enough to alter coagulation parameters. Ivermectin should be used with caution in individuals with immune compromise, asthma and during lactation.

The safety of the use of oral ivermectin in pregnant patients has not yet been evaluated (Please refer to pregnancy category B3, on the MIMS Gateway website). On the basis of animal study outcomes and given the availability of alternative topical management strategies for demodex and anterior blepharitis, use of ivermectin in pregnancy is not recommended.

As Demodex-associated blepharitis is not an approved use for ivermectin in New Zealand, and topical therapy (tea tree oil) is available and have been found to be effective, it is suggested that topical agents are used as first-line treatments.

Please note: The contraindications, precautions, interactions, and potential adverse effects listed for all medications (both topical and oral) in this document are <u>not exhaustive</u>. If required, the optometrist should seek further clarification from online sources (for example: Medsafe, NZ Formulary), or the patient's other healthcare provider(s) prior to prescribing these medications.

Review

There are no specific guidelines for follow-up of patients with anterior or posterior blepharitis, and the review period will depend on the severity of the presentation. Follow-up visits are required for all patients to monitor treatment efficacy and patient compliance with the treatment regimen.

Referral criteria

Generally, blepharitis does not require referral for ophthalmological opinion. Co-management with an ophthalmologist should be considered for severe cases with significant corneal involvement. Patients with neuropathic pain, where dry eye symptoms are vastly out of proportion to severity of the clinical signs, may benefit from referral to a chronic pain specialist.

Informed consent

As with all healthcare interventions, the optometrist is responsible for ensuring that the patient has been advised of the possible risks and benefits associated with the prescribed medication, in order that the patient can make an informed decision and provide consent to the treatment plan.

References

Albietz, J.M., Lenton, L.M. (2006). Effect of antibacterial honey on the ocular flora in tear deficiency and meibomian gland disease. Cornea, 25:1012-1019.

Albietz, J.M., Schmid, K.L.(2017). Randomised controlled trial of topical antibacterial Manuka (Leptospermum species) honey for evaporative dry eye due to meibomian gland dysfunction. Clinical and experimental optometry, 100:603-615

Blackie, C.A., Carlson, A.N., Korb, D.R. (2015). Treatment for meibomian gland dysfunction and dry eye symptoms with a single-dose vectored thermal pulsation: a review. Current opinion in ophthalmology, 26:306-313

Bowling B. (2016). Kanski's Clinical Ophthalmology (8th ed.): Elsevier

Castellsague, J., Kuiper, J.G., Pottegard, A., Anveden Berglind, I., Dedman, D., Gutierrez, L., Calingaert, B., van Herk-Sukel, M.P., Hallas, J., Sundström, A., Gallagher, A.M., Kaye, J.A., Pardo, C., Rothman, K.J., & Perez-Gutthann, S. (2018). A cohort study on the risk of lymphoma and skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids (Joint European longitudinal lymphoma and skin cancer evaluation - JOELLE study). Clinical epidemiology, . 10.2147/CLEP.S146442

Craig, J.P., Nelson, J.D., Azar, D.T, Belmonte, C., Bron, A.J., Chauhan, S.K., de Paiva, C.S., Gomes, J.A.P., Hammitt, K.M., Jones, L., Nichols, J.J., Nichols, K.K., Novack, G.D., Stapleton, F.J., Willcox, M.D.P., Wolffsohn, J.S., & Sullivan, D.A. (2017). TFOS DEWS II Report Executive summary. Ocular surface, 15:802-812. https://doi.org/10.1016/j.jtos.2017.08.003

Craig, J.P., Chen, Y.H., Turnbull, P.R. (2015). Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction. Investigative ophthalmology and visual science, 56:1965-1970.

Craig, J.P., Muntz, A., Wang, M.T., Luensmann, D., Tan, J., Huarte, S.T., Xue, A.L., Jones, L., Willcox, M.D.P., Wolffsohn, J.S. (2021) Developing evidence-based guidance for the treatment of dry eye disease with artificial tear supplements: A six-month multicentre, double-masked randomised controlled trial. Ocular surface, 20:62-69

Cheng, A.M., Sheha, H., Tseng, S.C. (2015). Recent advances on ocular Demodex infestation. Current opinion in ophthalmology, 26:295-300

Erdinest, N., Solomon, A. (2014). Topical immunomodulators in the management of allergic eye diseases. Current opinion in allergy and clinical immunology, 14:457-463

Filho, P.A., Hazarbassanov, R.M., Grisolia, A.B., Pazos, H.B., Kaiserman, I., Gomes, J.A. (2011) The efficacy of oral ivermectin for the treatment of chronic blepharitis in patients tested positive for Demodex spp. British journal of ophthalmology, 95:893-895

Finis, D., Konig, C., Hayajneh, J., Borrelli, M., Schrader, S., Geerling, G. (2014). Six-month effects of a thermodynamic treatment for MGD and implications of meibomian gland atrophy. Cornea, 33:1265-1270

Foulks, G.N., Borchman, D., Yappert, M., Kim, S.H., McKay, J.W. (2010). Topical azithromycin therapy for meibomian gland dysfunction: clinical response and lipid alterations. Cornea, 29:781-788

Gao, Y.Y., Di Pascuale, M.A., Li, W., Liu, D.T., Baradaran-Rafii, A., Elizondo, A., Kawakita, T., Raju, V.K., Tseng, S.C.G. (2005). High prevalence of Demodex in eyelashes with cylindrical dandruff. Investigative Ophthalmology and Visual Science, 46:3089-3094 https://doi.org/10.1167/iovs.05-0275

Geerling, G., Tauber, J., Baudouin, C., Goto, E., Matsumoto, Y., O'Brien, T., Rolando, M., Tsubota, K, Nichols, K.K. (2011). The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Investigative ophthalmology and visual science, 52:2050-2064

Greiner, J.V. (2013). Long-term (12-month) improvement in meibomian gland function and reduced dry eye symptoms with a single thermal pulsation treatment. Clinical and experimental ophthalmology, 41(6):524-30

Greiner, J.V. (2016). Long-Term (3 Year) Effects of a single thermal pulsation system treatment on Meibomian gland function and dry eye symptoms. Eye and contact lens, 42:99-107

Hooks, M.A. (1994). Tacrolimus, a new immunosuppressant--a review of the literature. The Annals of Pharmacotherapy, 28:501-511

Holzchuh, F.G., Hida, R.Y., Moscovici, B.K., et al. (2011). Clinical treatment of ocular Demodex folliculorum by systemic ivermectin. American journal of ophthalmology, 151:1030-1034.e1031

Igami, T.Z., Holzchuh, R., Osaki, T.H., Santo, R.M., Kara-Jose, N., & Hida, R.Y. (2011). Oral azithromycin for treatment of posterior blepharitis. Cornea, 30:1145-1149

Jackson, W.B. (2009). Management of dysfunctional tear syndrome: a Canadian consensus. Canadian journal of ophthalmology, 44:385-394.

Jones, L., Downie, L.E., Korb, D., Benitez-Del-Castillo, J.M., Dana, R., Deng, S.X., Dong, P.N., Geerling, G., Hida, R.Y., Liu, Y., Seo, K.Y., Tauber, J., Wakamatsu, T.H., Xu, J., Wolffsohn, J.S., Craig, J.P. (2017) TFOS DEWS II Management and therapy report. Ocular surf, 15:575-628

Kashkouli, M.B., Fazel, A.J., Kiavash, V., Nojomi, M., Ghiasian, L. (2015). Oral azithromycin versus doxycycline in meibomian gland dysfunction: a randomised double-masked open-label clinical trial. British journal of ophthalmology, 99:199-204

Kemal, M., Sumer, Z., Toker, M.I., Erdogan, H., Topalkara, A., Akbulut, M. (2005). The Prevalence of Demodex folliculorum in blepharitis patients and the normal population. Ophthalmic

Epidemiology, 12:287-290Kircik, L.H., Del Rosso, J.Q., Layton, A.M., Schauber, J. (2016). Over 25 years of clinical experience with ivermectin: An overview of safety for an increasing number of indications. Journal of drugs in dermatology, 15:325-332

Korb, D.R., Greiner, J.V. (1994). Increase in tear film lipid layer thickness following treatment of meibomian gland dysfunction. Advances in experimental medicine and biology, 350:293-298

Korb, D.R., Blackie, C.A. (2011). Meibomian gland therapeutic expression: quantifying the applied pressure and the limitation of resulting pain. Eye and contact lens: Science and clinical practice, 37:298-301

Lemp, M.A., Nichols, K.K. (2009). Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. Ocular surf , 7:S1-S14

Luchs, J. (2008). Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis. Advances in therapy, 25:858-870

Maskin, S.L. (2010). Intraductal meibomian gland probing relieves symptoms of obstructive meibomian gland dysfunction. Cornea, 29:1145-1152

McGhee, C.N., Dean, S., Danesh-Meyer, H. (2002). Locally administered ocular corticosteroids: benefits and risks. Drug safety, 25:33-55

Meisler, D.M., Raizman, M.B., Traboulsi, E.I. (2000). Oral erythromycin treatment for childhood blepharokeratitis. Journal of the American association for pediatric ophthalmology and strabismus (AAPOS), 4:379-380

Nelson, J.D., Shimazaki, J., Benitez-del-Castillo, J.M., Craig, J.P., McCulley, J.P., Den, S., Foulks, G.N. (2011). The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Investigative Ophthalmology and Visual Science, 2011;52:1930-1937

Nichols, K.K., Foulks, G.N., Bron, A.J., Glasgow, B.J., Dogru, M., Tsubota, K., Lemp, M.A., Sullivan, D.A. (2011). The international workshop on meibomian gland dysfunction: Executive summary. Investigative ophthalmology and visual science, 52 (4):1922-1929

Nichols, J.J., Berntsen, D.A., Mitchell, G.L., & Nichols, K.K. (2005). An assessment of grading scales for meibography images. Cornea, 24:382-388

Nazir, S.A, Murphy, S., Siatkowski, R.M., Chodosh, J., Siatkowski, R.L. (2004). Ocular rosacea in childhood. American journal of ophthalmology, 137:138-144

Perry, H.D., Doshi-Carnevale, S., Donnenfeld, E.D., Solomon, R., Biser, S.A., Bloom, A.H. (2006). Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea, 25:171-175

Rashid, S., Jin, Y., Ecoiffier, T., Barabino, S., Schaumberg, D.A., Dana, M.R. (2008). Topical omega-3 and omega-6 fatty acids for treatment of dry eye. Archives of ophthalmology, 126:219-225

Reinhard, T., Reis, A., Mayweg, S., Oberhuber, H., Mathis, G., Sundmacher, R. (2002). Topical Fk506 in inflammatory corneal and conjunctival diseases: A pilot study. Klin Monatsbl Augenheilkd, 219:125-131

Sakassegawa-Naves, F.E., Ricci, H.M.M., Moscovici, B.K., Miyamoto, D.A., Chiacchio, B.B., Holzchuh, R., Santo, R.M., Hida, R.Y. (2017). Tacrolimus ointment for refractory posterior Blepharitis. Current Eye Research, 42:1440-1444

Salem, D.A., El-Shazly, A., Nabih, N., El-Bayoumy, Y., Saleh, S. (2013). Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of Demodex folliculorum. International journal of infectious diseases, 17:e343-347

Schiffman, R.M., Christianson, M.D., Jacobsen, G., Hirsch, J.D., Reis, B.L. (2000). Reliability and validity of the Ocular Surface Disease Index. Archives of ophthalmology, 118:615-621

Shapiro, L.E., Knowles, S.R., & Shear, N.H. (1997). Comparative safety of tetracycline, minocycline, and doxycycline. Archives of dermatology, 133:1224-1230

Shoughy, S.S. (2017). Topical tacrolimus in anterior segment inflammatory disorders. Eye and vision, 4:7.

Sung, J., Wang, M.T.M., Lee, S.H., Cheung, I.M.Y., Ismail, S., Sherwin, T., Craig, J.P. (2018). Randomized double-masked trial of eyelid cleansing treatments for blepharitis. Ocular surf, 16:77-83

Tomlinson, A., Khanal, S, Ramaesh, K., Diaper, C., McFadyen, A. (2006). Tear film osmolarity: determination of a referent for dry eye diagnosis. Investigative ophthalmology and visual science, 47:4309-4315.

Wesolowska, M., Knysz, B., Reich, A., Blazejewska, D., Czarnecki, M., Gladysz, A., Pozowski, A., Misiuk-Hojlo, M. (2014). Prevalence of Demodex spp. in eyelash follicles in different populations. Archives of medical science, 10(2): 319–324

Wolffsohn, J.S., Aritam R., Chalmers, R., Djalilian, A., Dogru, M., Dumbleton, K., Gupta, P.K., Karpecki, P., Lazreg, S., Pult, H., Sullivan, BD, Tomlinson A, Tong L, Villani E, Yoon KC, Jones L, Craig JP. (2017). TFOS DEWS II Diagnostic Methodology report. Ocular surface, 15(3):539-574

Xue, A.L., Downie, L.E., Ormonde, S.E., Craig, J.P. (2017) A comparison of the self-reported dry eye practices of New Zealand optometrists and ophthalmologists. Ophthalmic and physiological optics, 37(2):191-201

Acknowledgements:

The Board thanks the following people for their contributions to developing the Board's oral medicine guidelines: Professor Nicola Anstice, Professor Jennifer Craig, Professor Helen Danesh-Meyer, Dr Simon Dean, Dr Hannah Kersten, Professor Charles McGhee and Mr Ross Tayler.

Approved by the Board: 2015 (V1)

Updated by Board: November (V3)

To be reviewed: 2025