Condition: 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 or mixed. The staphylococcal type 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.[1]

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.[2] Patients with early MGD may be asymptomatic, in which case the condition is considered subclinical. As the condition progresses patients are likely to become more symptomatic, reporting symptoms consistent with dry eye disease, and changes to the posterior lid margin occur.

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.[3] *Demodex folliculorum* are found predominantly in the lash follicles, while *demodex brevis* burrow into sebaceous and meibomian glands. When they inhabit eyelash follicles, Demodex mites can cause or exacerbate chronic anterior blepharitis. Demodex can lead to damage to the lid margin; they carry bacteria on their surface, causing blepharitis. In addition, the proteins inside the mites, and their products, are thought to trigger inflammatory responses, resulting in Demodex blepharoconjunctivitis.[4]

Significance

Chronic blepharitis is a common cause of ocular discomfort and irritation, and can adversely affect quality of life in affected individuals.

Prevalence

MGD is the leading cause of dry eye disease,[2] and up to 50% of patients seen in optometric practice show signs and/or symptoms of MGD.[5] Anterior blepharitis is a common ocular disorder, frequently encountered by optometrists in clinical practice, with approximately 15% of patients presenting with specific symptoms.[5]

Demodex infestation increases with age: 84% of the population aged 60, and 100% aged over 70 years exhibit Demodex infestation.[4] 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.[6]

Signs and Symptoms

Typical symptoms of blepharitis can include: [1]

- Burning/stinging sensation
- Grittiness
- Photophobia
- Crusting and redness of the lid margins
- Poor contact lens tolerance

Signs of blepharitis can include: [1]

- 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 slit lamp biomicroscopy. Cylindrical dandruff or sleeves are considered pathognomonic for ocular Demodex infestation [7]

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: [2, 4]

1. Administration of a validated dry eye questionnaire, e.g. the Ocular Surface Disease Index [8] (http://dryeyezone.com/documents/osdi.pdf) or the DEQ5 Questionnaire [4]

2. Calculation of blink rate and blink interval

3. Measurement of tear meniscus height
4. Non-invasive break-up time (NIBUT), whenever possible [4]
5. Measurement of tear osmolarity, if available [9]
6. Tear break-up time (TBUT) with minimal fluorescein (only if NIBUT not possible) [4]
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, expressibility and quality of meibum, and meibography to determine drop out [10]

The TFOS DEWS II diagnostic criteria state that OSDI symptoms score of ≥ 13 or a DEQ5 score ≥ 6 plus one or more positive sign (of 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.[11]

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 [12]
3. Aqueous deficient dry eye
4. Conjunctivitis (allergic, viral or bacterial)
5. Floppy eyelid syndrome

Management

Patient recommendations and over-the-counter management

1. **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,[13] have lost favour compared with

commercially available, dedicated lid cleansers which are more effective, do not cause ocular surface damage and are better tolerated.[14]

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).

2. **Warm compresses and lid massage**: 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 [13]. On-going application is required, and the optometrist needs to provide appropriate information and discuss the importance of compliance with their patients. ,

3. **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.[15] However, practitioners should caution patients against ingesting excessive doses of omega-3 fatty acids due to the possible anticoagulation effects.

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

5. **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.

6. **Manuka Honey Drops**: Topical application of Manuka honey eye drops can reduce lid margin bacterial load.[16] 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.[17]

In-office management

1. **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.[18] 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.

2. **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 eye and causes ocular 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.[19] This in-office treatment can be complemented with the daily use of lid hygiene measures as described above.

3. **Therapeutic gland expression**: This involves physical meibomian gland expression in order to achieve a therapeutic improvement. 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.[20] 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.[21] 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.[21]

4. **Thermal pulsation (LipiFlow®):** This involves heating the meibomian glands to 42.5 °C during a single, 12 minute, in-office procedure. The LipiFlow® treatment has been shown to be safe and effective for the sustained treatment of MGD,[22] some effects of which may persist for months or years.[23, 24] 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 six months.[25]

5. **Intraductal Meibomian gland probing**: This involves penetrating the Meibomian gland orifice, perpendicular to the lid margin, with a 2 mm probe, under local anaesthesia.[26] The aim of this treatment is to mechanically open the Meibomian gland orifice and overcome ductal stenosis, leading to an improvement in MGD symptoms. Orifice haemorrhage is frequently noted during the procedure.[26] 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.

Topical pharmacological treatment

1. **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 [27], 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 (eg. Fusidic acid 1%, twice daily) [28].

2. **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.[29] 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 reduce risk of corticosteroid-related adverse effects, including increased intraocular pressure, and posterior subcapsular cataract.[30]

3. **Topical cyclosporine:** Although this medication is indicated primarily for aqueous deficiency, this may play some role in treating MGD, but the evidence is equivocal. In one small study of 33 patients, topical cyclosporine did not improve symptoms, but did decrease the number of blocked meibomian glands.[31] Cyclosporine eye drops can be prepared by a compounding pharmacy (cyclosporine 0.05%), or prescribed as Restasis under Section 29 of the Medicines Act 1981 (medical practitioners only). Section 29 medications cannot be prescribed by optometrists in New Zealand: These medications are not approved for a specific use and can only be prescribed by a medical practitioner. For more information about Section 29 medications, visit https://medsafe.govt.nz. The prescription of compounded cyclosporine 0.05% eye drops is not restricted to medical practitioners, however, it is not subsidised. The prescription of topical cyclosporine is reserved for when conventional treatments have been unsuccessful, and in most cases, treatment with cyclosporine will be initiated by an ophthalmologist.

4. **Tacrolimus ointment**: Also known as FK506, tacrolimus is a calcineurin inhibitor with potent immunosuppressive properties.[32] Tacrolimus has a similar mechanism of action to cyclosporine; it blocks IL-2 production, thereby inhibiting further T-lymphocyte proliferation.[32] Prepared as an ointment, this drug has shown good penetration through corneal and conjunctival tissue and effective reduction in clinical signs of inflammation for patients with atopic blepharokeratoconjunctivitis.[33] Tacrolimus is therefore gaining interest as a therapy to control ocular surface inflammatory disease.

   Topical tacrolimus, available as compounded ophthalmic ointment or eye drops (various concentrations), 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.[34] 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 [35]. Treatment duration varies, but is generally 14 to 30 days.[34]

   Tacrolimus ointment is generally well tolerated and safe, and adverse effects are usually minor (transient ocular surface irritation in approximately 50% of patients [36]). Serious adverse effects are rare. However, a recent European multicentre study [37] 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 smaller associations for melanoma and non-melanoma skin cancer.

Oral pharmacological treatment

1. **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 – 100mg once daily, for 3 months (i.e. much lower daily dose than the therapeutic antibiotic dose).[29] 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.[38]

2. **Macrolides eg. azithromycin:** These medications 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.[39]

   Current oral azithromycin prescribing protocols for posterior blepharitis vary, and there is not universal agreement. One recommended regimen is 500 mg on day one with 250 mg per day for the following four days (a five day course). This has been shown to have a similar effect on patient symptoms, and improved clinical signs, compared with a one-month course of doxycycline (200 mg per day).[40] Alternatively, a pulsed dosage has been suggested, with oral azithromycin prescribed at 500 mg per day for 3 days in 3 cycles, with an interval of 7 days between each cycle.[41]

   Oral erythromycin has demonstrated efficacy in children with ocular rosacea [42] and blepharokeratitis,[43] 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.[43]

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 weighing risks and benefits. There have also been isolated reports of central nervous system disturbance including confusion, hallucinations, tinnitus, seizures and vertigo following macrolide use.

3. **Ivermectin**: An anti-parasitic agent with anti-inflammatory activity.[44] 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.[45] Ivermectin has been shown to reduce the number of Demodex mites found in the lashes of patients with chronic Demodex-associated blepharitis.[46, 47]

   In New Zealand, Ivermectin is available as Stomectol® 3 mg tablets. In two published studies, patients received two doses, one week apart, of 200 µg per kg of body weight.[45, 46] 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.[47]

   Side effects of oral ivermectin are usually minor. They can include flushing, nausea, lightheadedness, diarrhea, headache, joint pain and transient tachycardia.[46] 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 women has not yet been evaluated [pregnancy category B3 on MIMS Gateway (http://www.mims.co.nz/MIMSGateway.aspx)]. 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.

It should be noted that 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 blepharitis, and the review period will depend on the severity of the presentation. Follow-up visits are required for all patients in order 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.

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.

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Optometrists and Dispensing Opticians Board
Te Poari o ngā Kaimātai Whatu me ngā Kaiwhakarato Mōhiti

These guideline documents are not exhaustive and should be considered 'living' documents that will be added to over time. Conditions outside those described in these guidelines may be deemed out of scope for independent optometric management and require referral to a medical practitioner. If in doubt, please check with the Board for advice.

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