Recent advances on ocular Demodex infestation

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Purpose of review
To summarize recent advances on ocular Demodex infestation.

Recent findings
Demodex infestation is a potential cause of ocular surface inflammation. The pathogenesis of Demodex in eliciting ocular surface inflammation has been further clarified. Cliradex is currently the treatment of choice, it comprises the most active ingredient of tea tree oil, that is terpinen-4-ol, which helps eradicate Demodex mites and reduce ocular surface inflammation.

Summary
Ocular demodicosis is a common but overlooked eye disease that manifests a number of morbidities. Demodex folliculorum causes chronic anterior blepharitis whereas Demodex brevis causes posterior blepharitis, meibomian gland dysfunction, recurrent chalazia, and refractory keratoconjunctivitis. The lash sampling and microscopic counting method and in-vivo confocal microscopy are key diagnostic methods. Cliradex shows promising potential to reduce Demodex counts with additional antibacterial, antifungal, and anti-inflammatory actions.

Keywords
blepharitis, Cliradex, Demodex, meibomian gland dysfunction, ocular surface inflammation

INTRODUCTION
Demodex infestation is a common but overlooked cause of ocular surface inflammation. The prevalence of Demodex infestation increases with age, being observed in 84% of the population at age 60 years and in 100% of those older than 70 years [1]. The modified eyelash sampling and counting method and in-vivo confocal microscopy (IVCM) are key diagnostic methods [2,3,4\textsuperscript{**}]. Cliradex contains the most active ingredient of tea tree oil (TTO), that is terpinen-4-ol, which helps eradicate the mites and reduce ocular surface inflammation [5]. The present article summarizes recent advances in the diagnosis and treatment of ocular Demodex infestation.

PATHOGENESIS
The life cycle of the Demodex mite is approximately 14–18 days from the egg to the larval stage followed by the adult stage (Fig. 1) [6]. The life span of the mites is limited outside the living body and direct contact is required for trans-infestation. Two distinct species of Demodex mites have been identified in humans: Demodex folliculorum (Fig. 1a) and Demodex brevis (Fig. 1b). The D. folliculorum measures about 0.3–0.4 mm long and is primarily found in clusters around the root of the lashes and lash follicles, whereas the D. brevis measures about 0.2–0.3 mm long and resides solitarily in the sebaceous and meibomian glands [7]. Consequently, D. folliculorum is implicated in causing anterior blepharitis whereas D. brevis in posterior blepharitis, meibomian gland dysfunction, recurrent chalazia, and refractory keratoconjunctivitis [7,8]. The latter notion is supported by our recent study, which demonstrated a strong correlation between high prevalence of D. brevis infestation and chalazia [9\textsuperscript{**}].

During their lifespan, mites consume the lining of the hair follicles and lay eggs there, resulting in follicular distention and mal-directed lashes [10]. Debris and waste generated by mites accumulate at the root of the lashes forming cylindrical dandruff, which is pathognomonic for mites infestation [2,11–13]. Mites also mechanically block the sebaceous ducts, irritate the eyelid margin, and induce epithelial hyperplasia and hyperkeratinization.
The cytoskeleton of the mites may act as a foreign body and cause granulomatous reaction as implicated in chalazia [9**,15] or may elicit an inflammatory, immune response [14,16].

Recent studies revealed a potential relationship between demodicosis and microbial blepharitis by different mechanisms. First, the mites may work as a vector carrying bacteria such as staphylococci and streptococci, which are common causes of anterior blepharitis. Superantigens produced by these bacteria are also implicated in the induction of rosacea [17]. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been detected on eyelids of patients with *Demodex* infestation [18]. Although systemic antimicrobial therapy is effective for curing ocular inflammation in some meibomitis-related keratoconjunctivitis [19,20], it still remains unclear whether there is concomitant microbial involvement in *Demodex* infestation. The relationship between MRSA and ocular demodicosis requires further study. Secondly, mites can harbor symbiotic microbes in their intestines such as *Bacillus oleronius*, which has been found to trigger a host immune reaction by producing pro-inflammatory bacterial proteins that can stimulate proliferation of peripheral blood mononuclear cells in patients with rosacea [21]. Our prospective control study further disclosed a strong correlation among positive serum immunoreactivity to the 83 and 62-kDa bacillus proteins, ocular *Demodex* infestation, facial rosacea, and blepharitis [22,23]. In a total of 59 patients prospectively and consecutively enrolled, positive serum immunoreactivity had a significant correlation with facial rosacea ($P = 0.009$) and ocular *Demodex* infestation ($P = 0.048$).

**CLINICAL MANIFESTATIONS**

*Demodex* infestation in the face and eyelid has been implicated in causing rosacea [24–26] and blepharitis, respectively [11,27–29]. Such blepharitis frequently is associated with mite-harboring cylindrical dandruff in eyelashes [2]. Patients with *Demodex* induced rosacea have been clearly shown to have a higher *Demodex* density than controls [25,26,30,31]. However, no research has convincingly demonstrated whether a minimal number of mites must be present to produce symptoms. Moreover, there is no strong correlation between the severity of symptoms and signs and the extent of

**KEY POINTS**

- Suspect *Demodex* infestation in refractory blepharitis, trichiasis, chalazia, blepharoconjunctivitis, and keratitis.
- Lash sampling with microscopic counting method and in-vivo confocal microscopy are key diagnostic methods.
- Cliradex is the treatment of choice.

**FIGURE 1.** *Demodex* mites morphology. An adult *Demodex folliculorum* has a body-to-tail ratio of 1:2 (a), *Demodex brevis* has a body-to-tail ratio of 1:1 (b), larva has poorly developed legs (c), and a cone-shaped egg (d).
cylindrical dandruff or the Demodex count [8,11–13, 32,33*]. Such a discrepancy sheds light on other pathogenic elements that are variable among patients with ocular demodicosis.

Symptomatic patients usually present with itching, redness, burning, foreign body sensation, eyelid crusting, and blurry vision. These symptoms are more aggressive in patients with posterior blepharitis in which the inflammation spreads over to the conjunctiva producing blepharoconjunctivitis. As mentioned above, posterior blepharitis is associated with D. brevis and is usually refractory to conventional medications, especially in pediatric populations [34]. In addition, Demodex infestation may cause unexplained keratitis, superficial corneal vascularization, marginal infiltration, phlyctenule-like lesions, and nodular corneal scarring [8,35]. These corneal manifestations are commonly associated with D. brevis as it resides closer to the cornea and is prone to induce ocular surface inflammation [35].

DIAGNOSIS
It is important to suspect Demodex infestation in all patients with chronic blepharitis or refractory ocular surface inflammation. This is particularly pertinent in dealing with clinical problems associated with recurrent trichiasis, blepharitis, chalazia, conjunctivitis, blepharoconjunctivitis, and keratitis that are refractory to conventional treatments. Slit-lamp examination is used to detect cylindrical dandruff at the root of the lashes, which is pathognomonic for Demodex blepharitis [2,11–13]. Lash sampling and microscopic examination provide a definitive diagnosis by identifying the mites in the lashes with cylindrical dandruff [2,3]. It allows superior evaluation of the mite species and identification of the life stage, that is ovum, larva, protonymph, nymph, or adult (Fig. 2). Recently, IVCM has been used as a noninvasive method to diagnose Demodex infestation [4**,36] and allows a complete examination of the follicle with detecting the indistinguishable D. brevis, which burrows deep into sebaceous glands. However, the use of IVCM for the analysis of structures of the eyelids, meibomian glands, or the conjunctiva remains challenging because of the high reflectivity of substantia propria. Furthermore, comparative or innovative studies are needed to confirm the value of IVCM in diagnosing Demodex infestation especially in giving reliable quantitative assessment.

TREATMENT
TTO has been effectively used to eradicate ocular Demodex infestation [8,37,38]. Daily lid scrub with

![Figure 2](image_url)
50% TTO was also effective in resolving ocular symptoms and inflammation in the lid margin, conjunctiva, and cornea and significantly stabilizing the lipid tear film and improving the visual acuity [8]. However, the application of TTO was not convenient for self-administration and caused irritation in some patients [8,35,37]. Recently, terpinen-4-ol (T4O) has been identified as the most active ingredient in TTO that can eradicate mites with minimal side-effects [5]. The potency of T4O was greater than TTO at an equivalent concentration and possesses anti-inflammatory [39,40], antimicrobial [41–45], and antifungal [46,47] properties. Such effects have shown promising treatment effects for hospital-acquired infections and ocular surface infections, including MRSA [44,48,49].

The above-mentioned discovery has led to the development of Cliradex and Cliradex Complete (Bio-Tissue, Inc., Miami, FL, USA; Fig. 3). Cliradex is a lid hygiene wipe that contains T4O and can be self-administered by the patient. This facilitates the treatment of a number of ocular, and cutaneous diseases, caused by demodicosis that may be associated with or without concomitant bacterial or fungal infections. Recently, Cliradex Complete was developed for in-office application that boasts a stronger concentration of the isolated T4O than the existing Cliradex. Cliradex Complete, a lid hygiene kit, allows the initial treatment in-office by thorough cleaning of the root of the lashes and removal of debris from the lid margin. The kit also includes Cliradex for the patient to take home. The recommended treatment regimen is to apply Cliradex twice a day for at least 6 weeks to cover two Demodex life cycles. Patients may continue using a maintenance dose of once a day for a longer period of time to ensure mites eradication and to prevent re-infestation by mites migrating from other places of the body. The integrated lid hygiene helps manage symptoms associated with Demodex blepharitis, meibomian gland dysfunction, rosacea, dry eye, chalazia, and other lid margin diseases.

**CONCLUSION**

Demodex mite plays an important role in the recurrence of a series of refractory ocular surface diseases such as blepharoconjunctivitis, chalazia, meibomian gland dysfunction, dry eye, and keratitis. It remains unclear whether *D. folliculorum* and *D. brevis* may have different pathogenic roles in the lash follicle and meibomian gland, respectively. Diagnosis of ocular demodicosis can be made by either lash sampling with microscopic counting examination or in vivo by confocal microscopy although the best quantitative detection method for *Demodex* is still under investigation. Cliradex, formulated wipes...
soaked with T4O, is currently the treatment of choice for Demodex infestation.

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Conflicts of interest
Dr S.C.G.T. is an inventor, shareholder, and employee of TissueTech, Inc. He has filed two patents for the use of tea tree oil and its ingredients for treating demodexosis. No other authors have any proprietary interest in any material mentioned in this study.

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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:

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This study introduced WCM as a novel noninvasive diagnostic tool for Demodex infestation.

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This study demonstrated a strong correlation between Demodex brevis and multiple chalazia.


This study highlights the discrepancy between Demodex count and the severity of symptoms.

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