The Evolving Landscape of Demodex Blepharitis Management

HIGHLIGHTS

» Unmet Needs in the Management of Demodex Blepharitis

» Understanding the Prevalence of Demodex Blepharitis in US Eye Care Clinics: A Q&A With Paul M. Karpecki, OD, FAAO

» Determining the Impact of Demodex Blepharitis on Patients: A Q&A With Mitchell A. Jackson, MD

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DEMODEX BLEPHARITIS MANAGEMENT

Unmet Needs in the Management of Demodex Blepharitis

**DEMODEX BLEPHARITIS IS A** common inflammatory eye condition involving the skin, eyelashes, lash follicles, and sebaceous glands that is often overlooked.1,3 The disease is associated with infestation with *Demodex* mites, which are ectoparasites commonly found on human skin.4-6 Two distinct species of *Demodex* mites are found in both symptomatic and asymptomatic individuals: *D folliculorum* and *D brevis*.6 *D folliculorum* inhabits the margin of the lash follicle; it is associated with anterior blepharitis. *D brevis* burrows deep into the sebaceous glands at the base of the lash line; it is associated with posterior blepharitis.1,7

Symptoms are nonspecific to *Demodex* blepharitis and may include swollen and irritated eyelids, ocular burning, itching, foreign body sensation, crusting, matting, and loss of eyelashes.8,9 Secondary manifestations include rosacea, chalazion, meliobomian gland dysfunction, trichiasis, dry eye disease, keratitis, and inflammatory conjunctivitis.10-12 *Demodex* mites can be identified using microscopic techniques (eg, slit lamp) and sampling and evaluation of individual lashes (Figure).4,9 Currently, there are no FDA-approved treatment options for *Demodex* blepharitis. Available management options are limited and commonly include tea tree oil or its active ingredient terpinen-4-ol, which may be included in eyelid cleansers.10 Treatment with this substance may take several weeks to be effective; however, it often is unsuccessful at fully eradicating *Demodex* mites.8 Further, use of tea tree oil can cause mild irritation and discomfort.8,11

Left untreated, *Demodex* blepharitis can lead to more serious corneal conditions that may lead to scarring and blindness.2,3 Despite its worldwide prevalence, *Demodex* blepharitis remains largely underdiagnosed and underappreciated.4,5,15 This article describes the clinical burden of *Demodex* blepharitis and the unmet needs for patients and practitioners, particularly with respect to the lack of effective treatments to improve ocular health and the impact on patient quality of life.

Incidence and Prevalence

*Demodex* mites may be present on the eye margin in healthy humans, but this presence causes blepharitis only in some cases.4,6 Studies of the incidence of *Demodex* blepharitis in the US population are limited. Results of a retrospective study of *Demodex*-induced collarettes showed that among 1032 patients who visited 1 of 6 US eye clinics, 57.7% had *Demodex* blepharitis; collarettes were observed in 69.1% of these cases.5

Additional estimates of worldwide prevalence of *Demodex* blepharitis exist, but vary widely.15 Studies from individual countries reported the presence of *Demodex* mites in 30% to 90% of patients with blepharitis.16-24

The difference in frequency of *Demodex* infestation between sexes appears to be small, if it even exists. In the US study described previously, men had a slightly higher incidence of collarettes (62.9%) than did women (54.5%).4 Worldwide, some studies also noted a slightly higher incidence of *Demodex* in men than in women, although no difference was found in most of the research.4,16,25-28

Several studies reported a higher prevalence of *Demodex* blepharitis in older adults.4,16,25,28,30 The results of 1 US study suggested that *Demodex* blepharitis was common in patients of all races, but more research is needed on racial, ethnic, and geographical differences in *Demodex* infestation.5,14 A search of MEDLINE, PubMed, EBSCO, Cochrane, PROQUEST, and Google Scholar in June 2022
revealed that there were no known studies measuring cases of *Demodex* blepharitis in commercial insurance, Medicare, or Medicaid databases. More research is needed to effectively evaluate the frequency of *Demodex* blepharitis in various patient populations.

**Economic Burden**

No economic studies on *Demodex* blepharitis have been published. However, economic data on dry eye disease is available; *Demodex* blepharitis has been reported in a majority of patients with dry eye disease and may be a precursor to this condition. The results of a study of the US economic burden of dry eye disease performed in 2011 showed that the condition was associated with a direct overall annual cost of approximately $3.84 billion and an indirect overall annual cost of about $55.4 billion. Even if *Demodex* blepharitis only contributes to a portion of dry eye disease cases, as found in the US collarettes study, related costs still could be substantial.

**Pathophysiology**

Healthy, asymptomatic people can harbor *Demodex* mites, but an overpopulation of these ectoparasites can lead to inflammation through damage to infested tissue. Proliferation of *Demodex* mites is more common in older patients due to several variables, including abnormal skin barrier (eg, reduced surface hydration), decreased immunity, and poor personal hygiene.

*D folliculorum* is found in clusters along the lash line, whereas *D brevis* more commonly is detected in sebaceous glands; both types of these mites consume cell components and oils. During this process, the mites are believed to release lipases to aid digestion of sebum that may cause irritation to the tissue due to subsequent release of fatty acids. Further, small abrasions caused by the mite’s claws may result in epithelial hyperplasia and keratinization around the base of the eyelashes, forming collarettes (ie, cylindrical dandruff) on the upper lid margin. These waxy cylindrical plugs are present in 100% of *Demodex* blepharitis cases.

*Demodex* mites also have been known to plug the meibomian gland orifices, which could lead to observed meibomian gland dysfunction and tear film disruptions in *Demodex* blepharitis. Clogging of the meibomian glands and sebaceous glands by *Demodex* mites may result in the formation of chalazia and granulomatous reactions; however, chalazia are not always present in *Demodex* infestation, and further studies are needed to assess this relationship.

Finally, *Demodex* mites may trigger blepharitis by acting as vectors for harmful bacteria, *Bacillus oleronius*, a pathogen also often seen in chronic blepharitis, may initiate an immune response in individuals with rosacea.

**Presentation**

These pathogenic processes of *Demodex* blepharitis commonly are associated with itching and redness. Further, patients with *Demodex* blepharitis report ocular pain and burning, foreign body sensation, dryness, lacrimation, purulence, irritation, loss of lashes, matted or crusty lashes, and blurry vision. Lid margin health can be affected by infection-induced inflammation, and ocular surface manifestations (eg, corneal damage, chalazion, trichiasis, keratitis, conjunctivitis, blepharoconjunctivitis) may occur due to the infection.

The symptoms and signs of *Demodex* blepharitis also can affect patients emotionally. Recently, in the Atlas study (part of the phase 2b/3 Saturn-1 clinical trial described below), 311 patients with *Demodex* blepharitis were surveyed to understand the psychosocial burden of the
specific skin characteristics (eg, oily, dry). Modifiable factors believed to encourage proliferation of the lashes at the lid margin. Demodex presence of blepharitis symptoms, although recent reports suggest that it made it difficult to wear makeup. Added time to their daily hygiene routine, and 34% said that it made driving at night difficult, 30% said that it determines the threshold of mite infestation that results in negative appearance to others. Patients also stated that blepharitis gave their eyes or eyelids a healthy and affected individuals. There is no standard to determine the presence of an adult mites, larvae, or eggs. ally accomplished by visual analysis. A common method includes the presence of an adult mites, larvae, or eggs. Although this method is commonly used to determine the number of mites, it has several limitations. For example, it underestimates the number of mites present, as they can float away in the added oil and be retained in the collarettes that remain in the eyelid after lash removal. Sodium fluorescein can enhance the microscopic visualization of mites by dissolving and expanding the collarettes, thereby improving visualization of embedded mites and resulting in a more accurate population sample. The presence of Demodex blepharitis can also be identified via slit-lamp identification of collarettes localized at the base of the lashes at the lid margin.

Risk Factors
Immune-related skin conditions are associated with an increased incidence of Demodex blepharitis. Facial rosacea most frequently is postulated to be related to Demodex infestation, and seborheic dermatitis also is reported to correlate with Demodex proliferation. Immunosuppressive agents (eg, steroids) and diseases such as HIV or leukemia that compromise immunity are associated with an increased incidence of Demodex blepharitis. However, it remains unclear whether changes in immunity allow for Demodex infestation or whether Demodex mites cause inflammatory disease. Modifiable factors believed to encourage proliferation of Demodex include poor hygiene, alcohol abuse, and specific skin characteristics (eg, oily, dry).

Underdiagnosis and Misdiagnosis
Diagnosis of and research concerning Demodex blepharitis are complicated, because the mite resides on both healthy and affected individuals. There is no standard to determine the threshold of mite infestation that results in blepharitis symptoms, although recent reports suggest that a change in even 1 fewer mite per lash is associated with clinical improvement in patients who have been diagnosed with the condition. The disease shares symptoms with other ocular disorders; thus, it is frequently overlooked as a potential diagnosis, especially because clinicians do not routinely screen presenting patients for Demodex mite infestation.

Results of the Atlas study indicated that 51% of patients had signs of blepharitis for at least 4 years; 52% reported experiencing symptoms frequently or all the time over the previous month. However, 58% of respondents reported never receiving the diagnosis even though symptoms led them to visit their doctor 2 to 6 times. Further, results of the US-based collarettes study described above determined that 44% of patients with collarettes were not diagnosed with Demodex blepharitis, suggesting a high rate of underdiagnosis and misdiagnosis. Addressing the issue of misdiagnosis and underdiagnosis in Demodex blepharitis is important; left untreated, the disease can result in punctate keratitis and corneal melting. Further, lack of a proper Demodex diagnosis can result in ineffective management options and disease progression and a possible increase in the cost of care. For example, management of severe Demodex blepharitis may require use of microblepharo-exfoliation, which costs approximately $150 per session and needs to be repeated 4 times per year.

Current Management Options
Common management options are available for Demodex blepharitis, but no single strategy is always effective for long-term Demodex eradication. Recommendations for managing patients with Demodex blepharitis are briefly discussed in the blepharitis clinical management guidelines offered by the College of Optometrists. Lid hygiene measures are advised to reduce symptoms and prevent relapse. These include lid cleansing to wipe away debris and improve symptoms and use of warm wet compresses to loosen collarettes and crusts in anterior blepharitis. Patients are advised to avoid cosmetics, especially eye liner and mascara. Cleansing options include microblepharo-exfoliation and OTC lid scrubs and wipes. Many of these products contain tea tree oil or its active ingredient terpinen-4-ol; these substances have acetylcholinesterase-inhibiting effects responsible for acaricidal activity to reduce the number of Demodex mites. Modifiable factors that also is an ingredient of many commercial blepharitis cleansers) has acaricidal effects. Of note, comorbid conditions may necessitate treatment.

Limitations of Current Management Options
Demodex blepharitis continues to be an undertreated disease with no FDA-approved treatment options.
Because no single management option currently fully eradicates Demodex mites, there are no specific guidelines or a standard of care. In the Atlas study, 81% of patients reported seeking treatment, but many discontinued the management options provided due to efficacy or tolerability issues or other reasons. In the US collarettes study, patients using tea tree oil and lid wipes continued to have Demodex blepharitis in 75% and 57% of cases, respectively, indicating that current management tools for this disease are largely ineffective.

Tea tree oil has low efficacy; further, it is poorly tolerated and associated with allergies, dermatitis, and ocular irritation. Indeed, the results of clinical studies on the use of tea tree oil– or linalool-containing commercial cleansers showed that blepharitis symptoms were not fully resolved, and Demodex mites were not fully eradicated.

Methods to prevent irritation caused by tea tree oil include instructing patients to be less vigorous when scrubbing their eyelids, diluting the tea tree oil with mineral oil, or applying scrubs and saline rinses that have a higher concentration of tea tree oil during an office visit. Despite these precautions, poor adherence to these therapeutic options due to discomfort is associated with low Demodex eradication rates. Lack of adherence is further complicated by the need for long-term lid hygiene measures to relieve symptoms.

### Treatments Under Investigation

Only a few randomized, clinical trials have been or are being performed to test the efficacy of therapies other than conventional tea tree oil (Table). Active ingredients in these products include the antiparasitic drug ivermectin used with the antioxidant and anti-inflammatory drug metronidazole and the acaricidal drug lotilaner.

<table>
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<tr>
<th>TABLE. RCTs of Alternative Treatments for Demodex Blepharitis⁶⁶,⁶⁸-⁷¹</th>
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<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>Oral ivermectin, 200 µg/kg + oral metronidazole, 250 mg</td>
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<td>TP-03 (lotilaner ophthalmic solution), 0.25%</td>
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<tr>
<td>Topical gel containing ivermectin, 0.1% + metronidazole, 1%</td>
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<tr>
<td>Topical ivermectin cream, 1%</td>
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<td>TP-03 (lotilaner ophthalmic solution), 0.25%</td>
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NA, not available; RCT, randomized clinical trial.
Conclusions and Unmet Needs

Demodex mites are a major contributor to blepharitis and other ocular diseases. Several studies have assessed the prevalence of Demodex blepharitis worldwide, but, as of August 2022, only 1 study did so in the United States, suggesting that this disease is overlooked in this country. Although the economic burden of Demodex blepharitis specifically is unknown, based on data for dry eye disease, the annual cost of Demodex blepharitis is likely substantial.

The paucity of research on the epidemiology of Demodex blepharitis is reflected in a lack of routine screening for Demodex mites and a lack of standardized criteria for diagnosing the disease. Likewise, there are no stand-alone guidelines for managing Demodex blepharitis. Current management options include products containing Demodex alone guidelines for managing blepharitis, a dearth of disease awareness, a lack of best diagnostic practices, and an absence of FDA-approved treatments remain as obstacles in the management of this ophthalmic condition.

REFERENCES


Understanding the Prevalence of Demodex Blepharitis in US Eye Care Clinics

A Q&A With Paul M. Karpecki, OD, FAAO

AJMC®: Can you walk us through your published findings regarding the real-world prevalence of Demodex blepharitis? Why is this an important disease to study?

KARPECKI: Demodex blepharitis is one of the more common forms of blepharitis, and there's no good treatment for it. Some 45% of people diagnosed with blepharitis reportedly experience infestation involving the Demodex genus; however, that percentage is probably low. When you start to look for the pathognomonic sign of Demodex blepharitis—collarettes at the base of the lashes—you see a considerable number of cases. Moreover, in a referral practice like mine, the prevalence is higher; more than 90% of blepharitis cases involve Demodex mites. This type of infestation is not easily treated, and patients who don't respond to therapy are referred to our clinic. We have treatments for blepharitis associated with staphylococcal or bacterial infection and for dermatologic cases (eg, seborrheic dermatitis), but we really don't have anything for Demodex infestation. There's a real need to both appropriately diagnose the condition and find ways to manage it.

AJMC®: Demodex mites are commonly found on human skin—even in healthy humans—and symptoms of Demodex blepharitis (eg, swollen and irritated eyelids, ocular burning) are not specific to this disease. How do you study this disease and its prevalence?

KARPECKI: Demodex mites are the most common ectoparasites detected on the human body. They are a natural pathogen, so to speak. Certain people experience infestation of the skin, which has been associated with rosacea. Others may experience Demodex infestation on their eyelashes that occurs in different forms. D folliculorum tends to concentrate or localize on the lashes and the lash follicle; it also eats skin cells. D brevis tends to get into the sebaceous glands and the meibomian glands of the eyelid that produce the oils for tear film.

We do not know why infestation doesn't occur on everybody. We are not sure whether it is related to genetics, race, or another cause, but we see Demodex mite infestation in almost all populations. It is also unclear how age affects disease prevalence. According to some publications, Demodex blepharitis is commonly detected in people of all ages; according to others, it becomes more common as we become older. In my experience, prevalence seems to increase with age. Regardless of why this normal pathogen gets out of control, infestation is related to complications like redness, erythema, matting, crusting, dryness, and grittiness of the eyes.

Those are all common symptoms for the various forms of blepharitis. Demodex blepharitis is unique, because the Demodex parasite gets into the follicles. The excrement, nits, and debris that is extruded by the mites shows up on the base of the lashes. This is partially because the mites live inside smaller hair follicles; as the lash grows out, that mixture is forced out of the follicles. This manifests as a clear or, sometimes, whitish sleeve at the base of
the lashes. No other form of blepharitis is associated with the development of this sleeve, making it pathognomonic for Demodex-related disease. The formation of this sleeve also helps with accurate diagnosis. While the physician is at the slit lamp, the patient simply has to look down. They do not need to close the eyelids, but rather just look down, and then a physician can see evidence of Demodex infestation at the base. That really separates Demodex blepharitis from other forms of the disease.

The symptoms and progression of Demodex blepharitis can also differ from those of other blepharitis types. Itching tends to be a more common symptom of Demodex blepharitis than of other types of the disease. Loss and thinning of lashes occurs more often with Demodex blepharitis than with some of the other types. And because this type of blepharitis is not very treatable, these conditions can advance and cause more inflammation. We often see more severe disease with Demodex blepharitis because of our lack of adequate treatments.

AJMC®: What were the findings from your study regarding the prevalence of Demodex blepharitis in the United States?

KARPECKI: Demodex blepharitis was found to be more prevalent than we anticipated. We analyzed data from ophthalmologists and optometrists in specialty practices, general practices, contact lens practices, and even surgical practices; we had quite a mix among the various physicians. Also, all comers had to be noted in this study, meaning that a provider could not exclude any patient, even if they were pediatric or geriatric. We taught the doctors how to look for collarettes; most providers knew how to look for them, but for some it was new. It’s a nice 5-second test. Looking at lashes using a slit lamp is already standard practice, so the only added step was to have the patient look down while the provider scans the base of the lashes. Participating physicians were to examine each patient.

The results showed that Demodex blepharitis does not only appear in patients with dry eye or rosacea, in whom we might have expected to find infestation. Demodex blepharitis appeared in patients being treated for glaucoma, cataract surgery, contact lenses, and even those who visited their provider for routine eye examinations for glasses. Some 58% of all comers had collarettes, the pathognomonic sign of Demodex infestation. Some 58% of all comers presented with Demodex blepharitis! That’s a surprisingly large number. I would have anticipated 58% of patients with dry eye or of certain subtypes would have presented with Demodex infestation, but this was 58% of patients of all types. Also, the study was conducted in the offices of various professionals, including subspecialists and general primary eye care providers. Because Demodex infestation was found in patients visiting their provider for many reasons and in such a wide variety of offices, we expect that this condition is very prevalent. They were fascinating data.

AJMC®: Did you find any notable demographic differences among affected patient populations?

KARPECKI: My assumption going into this study was that we would see a significantly greater incidence of Demodex blepharitis with age. I always assumed that Demodex infestation may be detected in 70% of people aged at least 70 years, 50% of those aged at least 50 years, and approximately 30% of those aged at least 30 years. At some time, I’d been taught that, or at least I had that assumption. We decided that we needed to look into that.

What was surprising was that the prevalence of Demodex infestation was consistent across all age groups. There was not a significant difference from 1 age group to the other. Statistically, prevalence was about the same for 20- to 30-year-olds as it was for 60- to 70-year-olds. That prevalence didn’t correlate with age was an interesting finding.

The second part of the study was also interesting. For example, a slightly larger percentage of contact lens wearers harbored Demodex. Obviously, among patients with blepharitis, 69% showed collarettes. Mixed conditions—meaning that patients also could have staphylococcal blepharitis—may have been involved, but the patients also had Demodex infestation. Some 65% of patients with glaucoma had Demodex blepharitis; that may reflect the prostaglandin analogues that we prescribe for glaucoma patients. Those drops tend to be proinflammatory, and that may promote infestation. I would have expected a 90% correlation or more among patients with rosacea, but that ended up being 60%; however, we had an unexpectedly small sample of patients with rosacea.

The key stand-up point was that there was a lot of consistency. Some 59% of patients with dry eye disease exhibited collarettes, as did 56% of those with cataracts or who were about to have cataract surgery. That may speak a little bit to patient age, although the ages of affected patients were across the board. Finally, 51% of contact lens wearers had collarettes. So Demodex blepharitis is prevalent among patients with many conditions, but especially among those using glaucoma medications, in whom 68% had collarettes. It was interesting to see that the range for contact lens wearers with blepharitis was always between 50% and 70%. It was large in those subtypes that we identified and above 50% across the board. I guess there’s logic for that. The prostaglandin analogues for glaucoma are proinflammatory; these highly inflammatory agents may promote overgrowth of something like a Demodex parasite. Dry eye makes sense, because the parasites—especially the brevis form—probably enter the meibomian glands, which
could damage those glands and lead to more dry eye. Patients with cataracts could represent a small percentage of the affected population, and comorbidities could be relatively common. But the incidences among other subgroups (eg, contact lens wearers, patients with rosacea) were still quite high.

**AJMC®:** Your study examined why patients given a diagnosis of *Demodex* blepharitis came to the clinic and the reasons for their visits. Can you share the results?

**KARPECKI:** In those patients with blepharitis, we primarily looked at what they were using for treatment. We already thought that tea tree oil was the better therapeutic option for patients with *Demodex* blepharitis. But we found that 75% of patients currently being treated with tea tree oil still had a significant prevalence of collarettes. What that first told us is that doctors were doing a good job of recognizing collarettes, which is why they treating patients with tea tree oil. You would not typically treat bacterial—and certainly not seborrheic or otherwise dermatologic—forms of blepharitis with tea tree oil. We found that 75% of people using tea tree oil still had significant collarettes present. They still had *Demodex* infestation. Perhaps, at mild or moderate levels or even across the board, tea tree oil could have some effect, but we didn't break it down to that point.

Second, we looked at patients who used standard lid wipes. These surfactant cleaners are thought of as antibacterial products, and could have been why those patients who used them had fewer collarettes. However, 57% of patients using lid wipes still had collarettes. If the doctor can differentiate the form of blepharitis—which seemed to be happening—and put patients on tea tree oil, that means that there is a higher incidence of *Demodex* blepharitis. That's why they've used the tea tree oil. They've identified the patient with the disease properly, but the tea tree oil is not clearing the problem.

We found a 51% prevalence of collarettes among patients who were coming in for contact lens examinations. That's how we recognized the prevalence among patients with glaucoma—we noted that 68% were using prostaglandin analogue drops. Sixty percent of those on dry eye therapies (eg, lifitegrast, cyclosporine) had collarettes. Among those using topical steroids, 50% had collarettes. Their reasons for visits helped us to calculate percentages and form subgroups. We still noted whether patients had, for example, meibomian gland dysfunction but weren't at a disease state. Among that group, 57% had collarettes.

In all cases, there was a very diverse group of examinations, but we still noted a very high prevalence of collarettes. There were 7 medical investigators at 6 different sites. Data were included for over 1000 patients. That's how we could assess patients coming in for cataract evaluation or for cataract surgery. For those individuals, the examination was not to evaluate the possibility of having blepharitis.

**AJMC®:** Study results also indicated that many patients with collarettes were misdiagnosed. Could you describe these results and what they suggest about the misdiagnosis or underdiagnosis of this disease in the United States?

**KARPECKI:** I've always been fascinated how, until we have a therapeutic for a certain disease, we tend to underdiagnose it. It doesn't make a lot of sense, because we still would give the diagnosis, even if we didn't have treatments that were extremely effective, so we could identify and treat those patients in the future. For the most part, we are taught to look for a condition if we have a therapy available to treat it. We don't have a therapy to prescribe for *Demodex* blepharitis at this point, and I don't think doctors know how to look for clues to make this diagnosis. They don't know how to differentiate it from other conditions. They are relatively good at diagnosing blepharitis, but they don't tend to differentiate the staphylococcal, dermatological, seborrheic, and *Demodex* infestation forms of the condition. That's why *Demodex* blepharitis is underdiagnosed. Seasoned practitioners will use the slit lamp for its diagnosis, but this practice is not universal.

Further, our medical coding system (ie, *International Classification of Diseases, 10th Revision*) lacks a specific code for *Demodex* blepharitis that's easily identified and recorded. Many patients are simply given a broad diagnosis, at best, and there's nothing that allows differentiation. Providers who detect *Demodex* blepharitis should record it that way, but most providers do not.

**AJMC®:** What are the consequences of misdiagnosis or underdiagnosis of *Demodex* blepharitis?

**KARPECKI:** That's very important. Many times, we may deal with a benign condition; not like glaucoma where someone can lose vision or become blind. I would include blepharitis with those types of benign conditions—providers are less concerned about treating it unless a patient is highly symptomatic. That's an error, and there are common consequences of not treating affected patients. I have patients who may not have symptoms of blepharitis, but I note the presence of collarettes. I have to treat them and resolve the issue, and I tell the patient that, too. I say, “If I don't treat this, it will progress and lead to long-term issues.” These include development of chronic immune-mediated dry eye disease; if those glands are significantly affected, patients will need anti-inflammatory agents, immunomodulators, and certain supplements, among other therapies, for the rest of their lives.
There is a point when dry eye disease becomes chronic and progressive and affects the oil glands, which are critical to maintaining tear film. Dry eye disease also can lead to Hordeola—or styes—and chalazion. Those are somewhat disfiguring if you have enough of them. The early stages of Hordeola are painful. Patients don’t like how they look, and multiple Hordeola affect the eyelid contour or proper apposition. In turn, improper apposition could lead to more dry eye and more disease formation. Exposure keratitis, in which the eyes don’t close properly, can lead to more eye exposure and corneal damage. Further, lash loss or thinning of lashes may occur; both men and women complain about how thin their lashes become, and they eventually lose their lashes. Some patients have scalloped eyelid margins, which involves atrophy of the glands. Demodex blepharitis is one of the more common culprits for these problems.

Dry eye related to Demodex blepharitis may affect a patient’s ability to wear contact lenses. It also may cause chronic inflammation, associated comorbidities, and other forms of blepharitis. Pterygium is a chronic inflammatory condition associated with a fibroblastic growth that eventually may cause significantly decreased vision. Patients don’t appreciate chronically red eyes and eyelids that make it look like they’ve been drinking, smoking, or crying. Those are just some of the consequences of not treating Demodex blepharitis.

**AJMC®:** What advice about screening for this disease do you have for clinicians?

**KARPECKI:** During a regular slit-lamp examination, simply have the patient look down. Look for these sleeves at the base of the lashes. You don’t need to do anything more complex than that. Clinicians have purchased microscopes to look at the lashes of patients having a red skin tone to determine the prevalence of Demodex infestation. Still, there is no need for anything more complex than a physician doing a slit-lamp examination of the lashes as a patient looks downward, and everyone has that equipment.

In addition, look for grittiness, irritation, and dryness of the eyes. When itching is mentioned, many practitioners commonly consider allergic conjunctivitis, since itching and allergies go together. However, good insight would include asking the patient the location of itching, since that manifestation of irritation is the most common symptom of Demodex blepharitis. If it’s in the canthi, it’s probably more allergic conjunctivitis in the corner. However, if the patient points to or shows the lash margin or the eyelid margin, then they typically are affected by Demodex infestation.

**AJMC®:** Studies of the incidence of Demodex blepharitis in the United States are limited. Additional estimates of the global prevalence exist but vary widely. Studies from individual countries report the detection of Demodex mites in 30% to 90% of patients with blepharitis. How can we learn more about this disease and its prevalence? What would you like to see from future studies?

**KARPECKI:** I’d love to see longitudinal studies that help us understand progression of the disease. A lot of clinical complications that have been described occur in our patients. That provides a clinical perspective of what we see in specific patient populations. Depending on the sort of studies that point to that progression, those studies would be clinically valuable. In addition, we have international studies on prevalence and subtypes related to age, but we need more of them. Doctors will start looking for Demodex blepharitis when treatments become available. Finally, the social and cosmetic impact—the psychosocial impact—on patients with this disease must be considered. Many times, the human component is overlooked by clinicians looking at the disease itself and ocular findings. Affected patients experience considerable effects that warrant a diagnosis and subsequent treatment.

**AJMC®:** Demodex blepharitis has been reported in a majority of patients with dry eye disease, and it may be a precursor to the disease. Do prevalence studies of Demodex blepharitis in dry eye disease provide a firm foundation to estimate the economic impact of this condition? If not, what factors might managed health care professionals consider as they estimate the economic burden of Demodex blepharitis?

**KARPECKI:** You can get an idea of it. There’s no doubt that tying prevalence to existing evidence is a central problem. There’s a lot of overlap that occurs between dry eye and
Demodex blepharitis gives us an estimate, but it goes beyond that. There are some patients with dry eye who avoid work and other people; they have that burden from that standpoint. That burden is greater among people with Demodex blepharitis. There is more of an impact on productivity, activity, and presenteeism or absenteeism. The disease probably would be underestimated by looking at patients with dry eye, because those with the worst symptoms more likely have Demodex blepharitis. We can get a little more specific to that group in terms of costs.

We have approved therapies for dry eye that work for some patients. We don’t have that for Demodex blepharitis. People may have to spend more money to try different things. More aggressive treatments, like intense pulsed light therapy, are very costly and not covered by insurance.

The burden from a financial standpoint is also greater in terms of the limited number of available treatments for these patients. We don’t have as many options as we would with dry eye disease. And treatments that work temporarily are quite costly and often are not covered by insurance. There are many other factors unrelated to the cost burden that include the time required to treat, the need to try different treatments, and the effectiveness of certain scrubs. Also, since we’re diagnosing slowly, we tend to have more severely affected patients who have a far greater burden than does a patient with dry eye who is getting a diagnosis early. More specific data on Demodex blepharitis and other types of the disease would be beneficial. Demodex blepharitis is far more debilitating to patients than are other forms in terms of the lash loss, visual effects, dry eye, and other symptoms. That alone involves a more significant financial burden.

AJMC®: Are there major takeaways from the study that you would like to highlight?

KARPECKI: We must look for Demodex blepharitis in all patient types. No patient subgroup studied had a significantly higher percentage of the condition than did the others. We want to consider all patients—from those seeking contact lenses to others investigating cataract surgery—instead of specifically focusing on individuals with ocular surface disease, dry eye disease, or symptoms that appear to be related to blepharitis.

The second key component is age. We may have falsely assumed that we’re going to see a dramatically greater incidence as patients get older. Actually, Demodex blepharitis presents among individuals in all age categories. Finally, the differential diagnosis is important; this disease must be differentiated from other conditions (eg, allergies), because itching is a common symptom. Further, we must scrutinize individual cases to differentiate Demodex blepharitis from other types of the condition; lid scrubs and surfactants are being used instead of something that targets the Demodex infestation. Because of the potential cosmetic, medical, and financial burden on patients with this chronic, progressive disease, we must make a diagnosis promptly and give patients hope for future treatments.

REFERENCES:
Determining the Impact of Demodex Blepharitis on Patients

A Q&A With Mitchell A. Jackson, MD

AJMC®: Demodex blepharitis has a high estimated prevalence in the United States. However, few US studies of this disease exist. Why is this disease so understudied here?

JACKSON: The main reason Demodex blepharitis is understudied is that we don’t have a good treatment for it—at least, we don’t have one yet. Hopefully, we will soon have a good treatment for this disease in the United States, based on the results of clinical trials and FDA approval.

Demodex blepharitis also can be hard to diagnose. Most eye care professionals forget to tell patients to look down [while performing the eye examination] to observe the upper lashes. We look at the eyes and the lower lids, but we forget to look at those upper lashes where the collarettes are located. Collarette presence defines infestation with Demodex mites for diagnostic purposes.

AJMC®: During the 2022 ASCRS [American Society of Cataract and Refractive Surgery] Annual Meeting held in April 2022, you presented the results of the Atlas Continuation study, which examined the clinical burden of Demodex blepharitis.1 Before the study, what was known about how this disease impacts patients?

JACKSON: Demodex mites, which are among the most common ectoparasites detected in humans, come in 2 forms. The first is D folliculorum, which are found in clusters in the lash root and lash follicle, where they feed on sebum and follicular epithelial cells. The second is D brevis, which are shorter in length, more solitary, and prefer to reside in the meibomian glands. D brevis is associated with blepharitis, meibomitis, meibomian gland dysfunction, recurrent chalazion, blepharokeratitis, blepharoconjunctivitis, and pterygium—all things on the ocular surface. That’s the impact it has in terms of the ocular world. D brevis has some implications in nonocular disease, as well, such as folliculitis rosacea, seborrheic dermatitis, perioral dermatitis, scalp hair loss, and even basal cell carcinoma. It has a lot of implications throughout the body besides just the ocular implications.

AJMC®: What prompted you to study Demodex blepharitis?

JACKSON: Currently, we use a variety of products to [manage] the disease, but these products are not indicated for the treatment of Demodex blepharitis. These products can work partially or on a short term, and they might give some symptom relief, but they may not eradicate the Demodex itself. The Atlas Continuation study’s main purpose was to evaluate the impact of Demodex blepharitis on visual function, daily activities, and motivations for seeking care.1 The investigators looked at the impact and burden of Demodex blepharitis on a patient’s quality of life and visual function. We wanted to know if it is really worth finding a treatment for Demodex blepharitis. We wanted to see if [the disease] is really impacting life, visual function, and daily activities in a way in which you really realize, “We have to look for a treatment for this, because there’s an impact.”
**AJMC®**: How did you select the patients for the Atlas Continuation study?

**JACKSON**: A total of 20 ophthalmic and optometric eye care professional centers in the United States were recruited for this observational study; clinicians at these centers screened for patients with *Demodex* blepharitis. The patient criteria included having at least 1 mite per lash, more than 10 collarettes, and mild or more severe erythema of the upper lid margin. Patients then filled out a questionnaire about symptoms, impact on daily living, and [disease] management experience.

The results of this Atlas Continuation study were presented at the ASCRS Annual Meeting; it is a continuation of the Atlas study presented at the 2021 ARVO (Association for Research in Vision and Ophthalmology) Annual Meeting, which included 311 patients. A total of 524 patients qualified and participated in this Atlas Continuation study with a mean age of 66 years (±14 years); 56.7% of the patients were women.

We found that patients were seeking care because no one was diagnosing [the disease], and these were symptoms patients were experiencing for at least 2 years. Patients were really struggling with the disease, but they were not being diagnosed. That’s the main thing. About 68% of patients experienced signs and symptoms of *Demodex* blepharitis over 2 years, 32% of patients saw their eye doctor at least twice, and 20% of these patients saw their doctor at least 4 times, yet nearly 60% never received a diagnosis of blepharitis or *Demodex* blepharitis.

This is why it’s so important for every eye care professional to have patients look down during their eye examinations to look for collarettes. It’s crazy how many patients experience signs and symptoms for that long without being diagnosed, and most of the patients had reported their symptoms. The top 3 symptoms reported were itchy eyes or eyelids, dry eye, and foreign body sensation. Some 55% of patients had itchy eyelids or itchy eyes, 46% had dry eye, and 23% had foreign body sensation. There were a variety of other symptoms as well—tearing, blurred vision, red eyes, gritty eyes,uffy eyelids, flaking from the eyelids, loss of eyelashes, and eyelids sticking together—but the top 3 were itchy eyes, dry eyes, and foreign body sensation.

This really showed us that patients had *Demodex* blepharitis, they were struggling, and no one was diagnosing it, never mind treating it. This is a good discovery. These study results really showed the need for diagnosis and a way to diagnose it. There will be a need for a treatment when eye care professionals are better trained to make the diagnosis.

**AJMC®**: How does *Demodex* blepharitis impact patients’ daily lives?

**JACKSON**: In the Atlas Continuation study, we observed that the most common burdens on patients were difficulty driving at night, which 47% of patients reported, and feeling conscious of their eyes all day, which also was reported by 47% of patients. This means that patients’ eyes itched or they felt like *Demodex* blepharitis caused a negative appearance of their eyes all day. Overall, 80% of patients said the disease negatively affected them in some way.1

Further, 34% of the women said that they had difficulty wearing makeup, and 30% of all patients said that they needed additional time for their daily hygiene routine, because their eyes required more care than did those of the average individual due to *Demodex* blepharitis.1 It definitely impacts their lives.

**AJMC®**: The Atlas Continuation study found that almost half the patients (46%) were using warm compresses or wipes, and almost half (47%) were using artificial tears. Still, 43% of patients had discontinued these or other treatments due to adverse effects or low efficacy.1 Is this consistent with your clinical experience?

**JACKSON**: Yes, because nothing is really treating *Demodex* blepharitis. In the study, the [management options] most people tried were lid wipes or tea tree oil, and almost everyone was already using artificial tears. Of all these [management options]—whether it was artificial tears, warm compresses, lid wipes, an antibiotic-steroid combination, tea tree oil, or an oral antibiotic like doxycycline, which is good for meibomian gland function—46% of patients who discontinued their regimen did so because of efficacy or tolerability issues. None of these options, as we discovered, are effective in mitigating or eliminating *Demodex* blepharitis. That’s the problem. These are all the [management options] we use now, because we don’t have anything else. This shows the need for the treatment, because these [management options] don’t work, patients

“The main reason *Demodex* blepharitis is understudied is that we don’t have a good treatment for it—at least, we don’t have one yet.”

—Mitchell A. Jackson, MD
DEMODEX BLEPHARITIS MANAGEMENT

aren't diagnosed properly, and it's affecting their lives and activities of daily living negatively.

The results of the Atlas Continuation study showed the psychosocial and functional impact of the disease. We have to continue with eye care professional education on how to diagnose Demodex blepharitis and make sure that it's getting diagnosed and not missed. Once we have a treatment for Demodex blepharitis, eye care professionals will be more likely to look for it, because they then will be able to treat it and hopefully say, "Hey, that's why some of these people aren't getting better! We've been [managing] it with all these other regimens, and the patients really had Demodex."

AJMC®: Given the multitude of products currently being used to manage Demodex blepharitis, what are the costs associated with the misdiagnosis of this disease?

JACKSON: If patients are coming back [to their providers] at least 2 to 4 times, there are additional costs. There is some ancillary testing associated with cost, such as tear osmolarity or dynamic meibomian imaging, and then there's the cost of pharmaceuticals, devices, thermal pulsation device treatments, or intense pulsed light. There are a lot of different [management options] being offered.

AJMC®: What could be the value of a treatment for Demodex blepharitis?

JACKSON: If 80% of patients in this Atlas Continuation study said that Demodex blepharitis affected them negatively in their activities of daily living, then a treatment could help improve quality of life for 80% of this population, in general. Visual function, such as night driving, was one of the biggest concerns, so [a treatment] could have a big impact.

REFERENCE


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Eye Care Products in the Pipeline for Demodex Blepharitis

A Q&A With Cynthia Matossian, MD, FACS

AJMC®: In your opinion, why are there no formal guidelines for Demodex blepharitis?

MATOSSIAN: Ophthalmologists and other eye care providers have known about Demodex blepharitis for a very long time. [The condition] involves an infestation or an overpopulation of Demodex mites at the base of the lashes and at the edge of the lid margins. We all have Demodex mites around different body parts, but when there's an overabundance of these little mites, they start to have a negative impact on the lid margin, on the lashes themselves, and on the ocular surface. We haven't had clear definitive treatment guidelines about this type of blepharitis because we haven't had a truly good treatment. Of course, we've known about ways to minimize the infestation or overpopulation of the Demodex mites, such as good lid hygiene—washing the edge or margin of the eyelids, removing mascara and other eye makeup before going to sleep, and taking good care of the periocular region.

AJMC®: In your experience, has the lack of guidelines impacted the diagnosis and management of Demodex blepharitis?

MATOSSIAN: Sometimes, when we don't have a very good treatment modality, we don't even bring up the underlying pathology. Why bring up a subject when we don't have a treatment for it? For example, decades ago, we didn't bring up dry eye disease, because the only treatments available were artificial tear solutions and ointments. We skipped over dry eye disease and discussed other diagnoses that the patient was given or that we made for that patient as we performed their eye examination. Demodex blepharitis is falling into the same pattern. Until now, we didn't have a good way to diagnose and treat it.

This disease is very prevalent, and it's significantly underdiagnosed, because eye care practitioners haven't gotten in the habit of looking for it, and they didn't have a tool or a treatment modality for addressing this epidemic disease. Now that a treatment is on the horizon, we can start to look for Demodex blepharitis.

What are some ways to look for this disease? Obviously, ask the patient for a history. Ask if their eyelid margins itch or become red, inflamed, and a little swollen. Ask if they are always rubbing their lashes because they're uncomfortable, and if there is burning and stinging of their ocular surface.

If the patient answers “yes” to some of those questions, then a careful a slit-lamp examination is all an eye care provider needs to do to make the diagnosis. Providers should have the patient look down a little bit, and then start to focus the joystick and the slit lamp on the lid margin at the base of the lashes. Look for little collarettes that almost look like turtlenecks around the base of the eyelashes. The collarettes may have different widths, but, if there's circular debris, that calamari-looking ringlet at the base of the lash is very characteristic of Demodex infestation.

Another telltale sign is misdirected lashes. If the normal swoop up of the lash with that very gentle curve is missing; if the lashes are sticking straight out,
downward, or in different directions; if lashes are slightly broken; or if there are missing lashes, *Demodex* infestation may be present.

**AJMC®:** In the absence of FDA-approved treatments, what constitutes the current standard management strategy for *Demodex* blepharitis?

**MATOSSIAN:** After the diagnosis of *Demodex* blepharitis is made, the only option we have is to educate the patient without scaring them. Providers should let the patient know that *Demodex* infestation is very common—they just have an oversupply of the mites. This condition can be [managed], but it often recurs. We can control it but not cure it forever, so to speak. With this information, the patient better understands what’s going on and what they need to do to keep the infestation and inflammation under control.

Tea tree oil is available in a variety of products. I often prescribe lid wipes that contain different concentrations of it. I prescribe towelettes with the highest concentration of tea tree oil; they come in individual foil pouches. I tell the patient to take 1 side of the towelette, close their eyes, and wipe back and forth, back and forth, at least 10 times on their lashes, and then move it onto their eyebrow. I instruct men with hairy ears also to clean the hairs in their ears. I tell my patients to flip the towelette to the clean side and do the same thing (again, with the clean side)—swipe back and forth 10 times on the eyelid margins, lashes, eyebrows, and ear hairs, and then discard the towelette. I tell them to repeat that every day for 60 days; you need a 2-month cycle to break the parasitic cycle of eggs being laid and hatched. Thereafter, the towelettes must be used the same way intermittently to keep the infestation under control. Importantly, application of tea tree oil stings, especially when used at that concentration. To minimize stinging and burning, patients must keep their eyes closed and count slowly to 25 or 30 before opening their eyes.

Another [management] option is in-office procedures, such as microblepharoexfoliation with a sponge using a prescription eyelid hygiene product—hypochlorous acid, tea tree oil, or a product that includes tea tree oil—while the sponge is rotating. This process debunks the *Demodex* mite load. It removes the biofilm at the base of the lashes, which the mites need as a food source. It also removes their regurgitated debris.

That in-office [procedure] often is needed every 4 months, every 6 months, or even once each year, depending on the severity of the situation. Again, that is customized to the patient’s needs. On the other hand, an at-home version is available that involves use of a handheld electric eyelid and eyelash brush with a viscous product that doesn’t spray all over the place. The product may or may not contain tea tree oil. Again, removal of debris every day or every other day minimizes the risk of mites building back up in quantity and causing deleterious adverse effects.

**AJMC®:** How effective are these tea tree oil–based products as management options, and how well do patients respond to them?

**MATOSSIAN:** Tea tree oil is the best option we have. There’s evidence that mechanical debridement done concomitantly with application of tea tree oil decreases the number of mites on the eyelids. But tea tree oil can sting and burn, which may discourage patients from continuing its use. Patients may use it for a short period of time, or they may not be very adherent. The over-the-counter products or the prescription products for wipes with a higher tea tree oil concentration represent the only good therapeutic option that we have had.

For me, [management] involves debulking with a mechanical in-office procedure, followed with an at-home debulking procedure on a daily or every-other-day basis, plus the tea tree oil.

**AJMC®:** Are there any treatments on the horizon?

**MATOSSIAN:** There are some products with excellent safety and comfort profiles in the preliminary studies. Lotilaner, which is now under investigation by Tarsus Pharmaceuticals here in the United States, hopefully will be available over the next 1 to 2 years. Instillation of 1 drop of this product into the eyes twice a day for a 6-week period may achieve no detection of collarettes at about 6 weeks. Of course, mites are on our bodies, and there is a chance of reinfection. The treatment may have to be repeated semiannually in patients who need it. This would be the first prescription product to treat *Demodex* blepharitis.

In the area of dry eye disease, ocular surface disease, and blepharitis treatment, therapies often are additive, and they’re layered 1 on top of the other. Very few are exclusive.
treatments, meaning it’s the only thing you use. I view Demodex blepharitis in a very similar fashion. Of course, if lotilaner is approved by the FDA, it will be a definitive prescription pharmacologic agent to treat Demodex mite infestation. At the same time, performing a debulking procedure in the office to remove biofilm, which is the food source for the mites, may help to provide comfort to the patient faster and help the pharmacologic agent work best by opening the orifices of the meibomian glands. Thus, the drug can penetrate and kill any of mites living inside the meibomian glands and at the base of the lashes. Use of the at-home remedies, maybe including a low concentration of tea tree oil for maintenance therapy at home, may discourage the quick buildup of Demodex mites. Use of the at-home microblepharoexfoliation treatment with an oscillating head also can help keep the lash base and lid margins healthy to minimize the overgrowth of mites. When there’s an overgrowth of mites, and symptoms become apparent, we can always re-treat with a prescription product. I see it as adjunctive therapy that may minimize the need for in-office treatments and that helps to keep the eyelids as healthy and the patient as comfortable as possible.

AJMC®: What should managed care providers know about current and forthcoming treatments for Demodex blepharitis?
MATOSSIAN: Demodex blepharitis is very common. Eye care providers should start looking for it. They will be very surprised at how commonly they are going to see the collarettes and the misdirected lashes of the patients in their offices. Most of the time, adherence drops off when treatment must be used chronically and multiple times a day. For example, patients with glaucoma need to use multiple products that must be instilled a few times a day, forever. The potential upcoming treatment for Demodex blepharitis is not like that. It’s expected to be used twice a day for 6 weeks. Once patients understand that there’s a light at the end of the tunnel, it’s very doable. Most patients can be adherent for a 6-week period.

Help is on the way, hopefully soon, with the FDA approval of a product that appears to be very promising. We will have a means to deliver care and treatment for our patients to help them with the discomfort that Demodex blepharitis can cause. Whether it’s itchy eyelids, red eyelid margins, telangiectatic vessels, burning, or stinging, the signs and symptoms of Demodex blepharitis may be improved with treatment.
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