Rapid Fire: Demodex Blepharitis: Prevalence, Burden, Current Management Approaches and Emerging Treatments

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Paul M. Karpecki, OD, FAAO Financial Disclosures:

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Surface Biopharma
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TearClear
Trukera
Vial
Viatris
Visant Medical
Vital Tears

relationships have been mitigated

Course Objectives

- Identify the prevalence, pathogenesis, and etiology of *Demodex* blepharitis
- Discover the comorbidities and clinical manifestations associated with *Demodex* blepharitis
- Learn how to identify and confidently evaluate signs/symptoms of *Demodex* blepharitis and how to distinguish them from other infectious and non-infectious signs, discharge, lash debris, and diseases
- Learn about the efficacy, tolerability challenges, and unmet needs of current management techniques for *Demodex* blepharitis, and discuss emerging treatment undergoing FDA trials

FDA, US Food and Drug Administration.

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Overview of Discussion

I: *Demodex* Blepharitis: An Introduction

II: Diagnosis and Prevalence

III: Clinical and Psychosocial Burden of *Demodex* Blepharitis

IV: Concomitant Disorders

V: Case Studies

VI: Current and Emerging Management Approaches

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Demodex Mites Are the Most Common Human Ectoparasites

- ***Demodex folliculorum*** **and** ***Demodex brevis*** **are the only 2 species of** ***Demodex*** **mites found in humans[1,2]**
- **The life cycle of the** ***Demodex*** **mite is approximately 14 to 18 days from the egg to the larval stage, approximately 5 days of which are spent as an adult[1,2]**
- **During their life cycle, adults reproduce and, in some patients, can result in** ***Demodex*** **infestation over time[3]**

Image courtesy of Scheffer Tseng, MD, used with permission.[4]

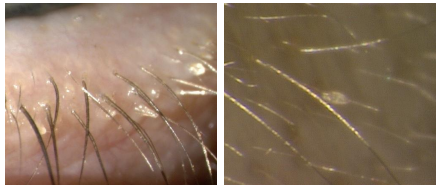
D. folliculorum

0.3 to 0.4 mm length
Colonizes the base and inside the lash follicle[2]

D. brevis

0.1 mm length
Colonizes the meibomian gland[2]

Image courtesy of Scheffer Tseng, MD, used with permission.[4]



Images courtesy of Ben Gaddie, OD, FAAO, used with permission.[5]

Demodex **mites can be found in any hair follicles with oil, including the face[3]**

1. Zhang AC et al. *Ophthalmic Physiol Opt*. 2020;40(4):389-432. 2. Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. 3. Lacey N et al. *Biochem (Lond)*. 2009;31(4):2-6. 4. Data on file. Images courtesy of Scheffer Tseng, MD; 2022. 5. Data on file. Images courtesy of Ben Gaddie, OD, FAAO; 2022.

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Demodex Blepharitis

- Blepharitis is the inflammation of the eyelids causing irritation and redness[1]
- 69% of blepharitis cases are due to *Demodex* infestation[1-4]
  - *Demodex* mites are implicated in other diseases of the lid and lid margin and meibomian gland dysfunction[2,3]
  - *Demodex* mites have a propensity for epithelial cells and oil dispensing glands as food sources[3]

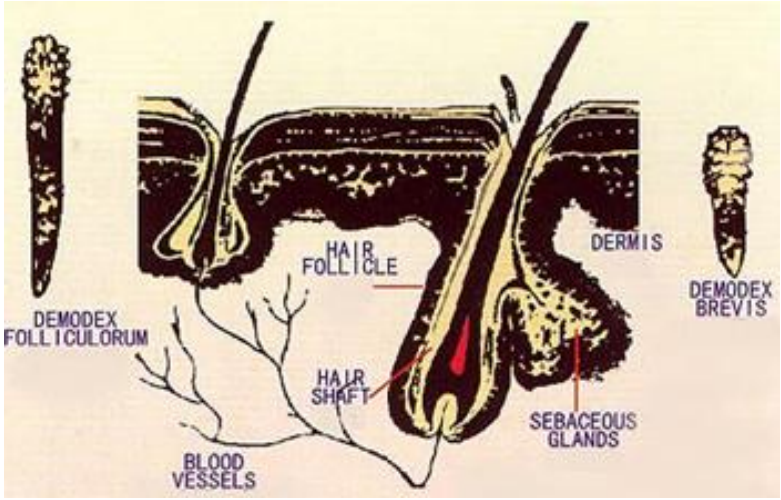

Image courtesy of *Demodex* Solutions.[5]

1. Mayo Clinic. Accessed September 26, 2022. https://www.mayoclinic.org/diseases-conditions/blepharitis/symptoms-causes/syc-20370141. 2. Zhang AC et al. *Ophthalmic Physiol Opt*. 2020;40(4):389-432. 3. Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. 4. Trattler W et al. *Clin Ophthalmol*. 2022;16:1153-1164. 5. *Demodex* Solutions. Accessed October 24, 2022. https://www.demodexsolutions.com/c/about-demodex/

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Myths/Notions Associated With *Demodex* Mites

- ***Demodex* mites are only active at night**
  - It is often stated that mites are most active at night; however, there is minimal research to support this statement
  - There is evidence that *Demodex* mites are photosensitive and avoid bright lights, but this does not mean they are not active during the daytime
- **Regular cleaning of towels or bedsheets can help manage infestation**
  - There is no evidence that washing bedsheets can mitigate symptoms in humans
- **Mites are transferred through direct contact**
  - *Demodex* mites are likely a normal part of our eyelid flora; how they are initially transferred to humans is unknown
- ***Demodex* mites are a result of poor personal hygiene**
  - Everyone likely has some level of *Demodex* mites
  - There is no clear correlation between hygiene and *Demodex* infestation

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Diagnosing *Demodex* Blepharitis: Collarettes as a Pathognomonic Sign

Collarettes, or cylindrical dandruff in the eyelashes, are a pathognomonic sign of *Demodex* blepharitis.[1,2]

- Collarettes are located around the base of the eyelash follicle and may also be found on the eyelash itself[1,3,4]
- Up to 25 mites per follicle have been demonstrated[5]

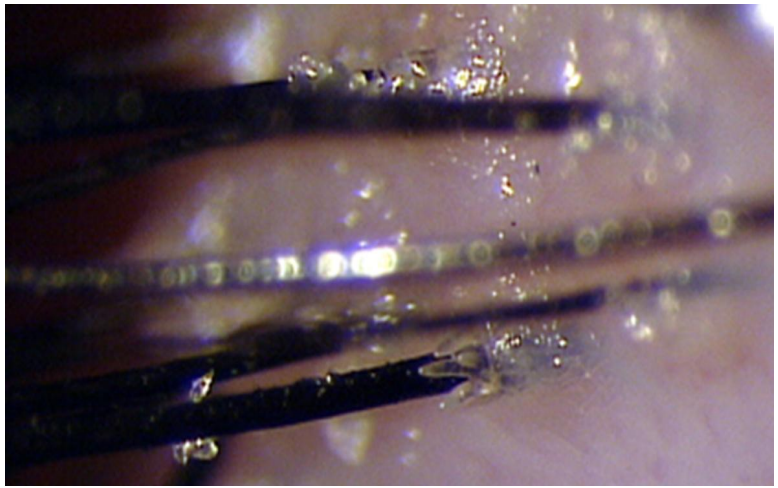

Image courtesy of Katherine Mastrota, MS, OD, EMBA, FAAO, used with permission.[6]

1. Kasetsuwan N et al. *Int J Ophthalmol*. 2017;10(1):122-127. 2. Gao YY et al. *Invest Ophthalmol Vis Sci*. 2005;46(9):3089-3094. 3. Zhang AC et al. *Ophthalmic Physiol Opt*. 2020;40(4):389-432. 4. Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. 5. UF/IFAS News Release. Accessed October 3, 2022. https://entnemdept.ufl.edu/pestalert/acne.htm. 6. Data on file. Image courtesy of Katherine Mastrota, MS, OD, EMBA, FAAO; 2022.

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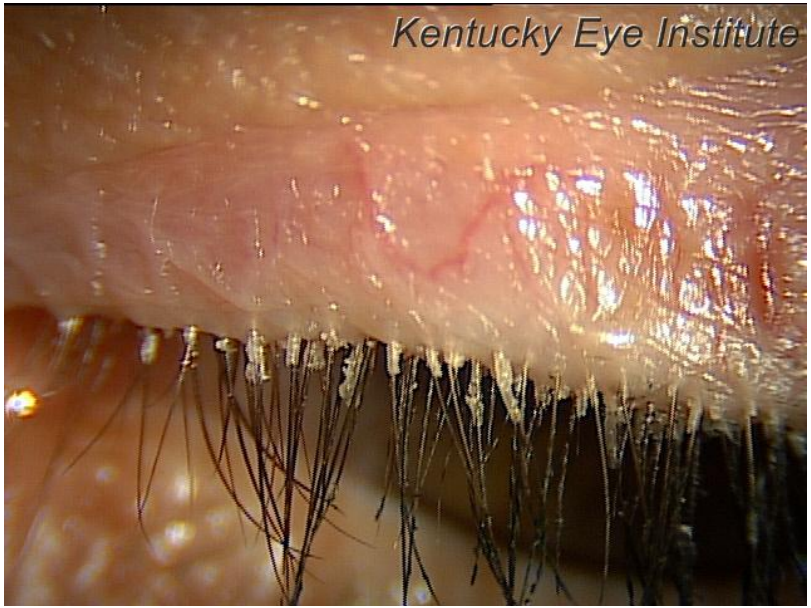
Making the Diagnosis

- The presence of collarettes can be used to confidently make a diagnosis of *Demodex* blepharitis[1,2]

- Collarettes can be identified through slit lamp examination, when the base of the lashes are exposed as the patient is instructed to look down[1,2,4,*]



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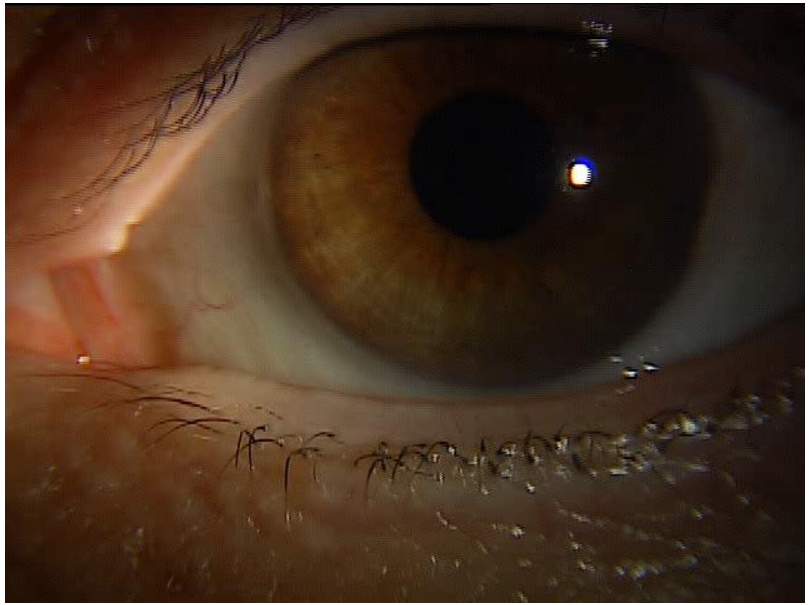
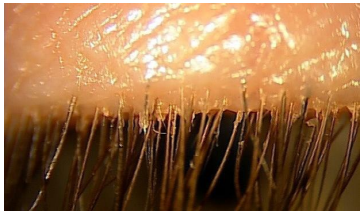
All That Is Needed for Diagnosis Is a Slit Lamp

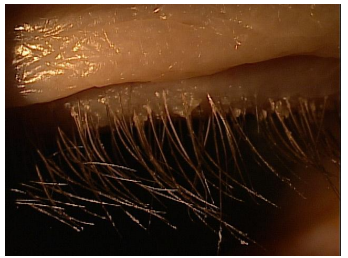
It is difficult to identify collarettes when the patient is looking straight ahead.[1-4]



A slit lamp examination will reveal:

- **Diffuse collarettes[1]**
- **Misdirected or missing lashes[2-4]**





1. O'Dell L et al. *Clin Ophthalmol.* 2022;16:2979-2987. 2. Zhang AC et al. *Ophthalmic Physiol Opt.* 2020;40(4):389-432. 3. Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089-3094. 4. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 5. Data on file. Image courtesy of Paul Karpecki, OD, FAAO; 2022. 6. Data on file. Image courtesy of Elizabeth Yeu, MD; Inder Paul Singh, MD, and Paul Karpecki, OD, FAAO; 2022. 7. Data on file. Image courtesy of Elizabeth Yeu, MD; 2022.

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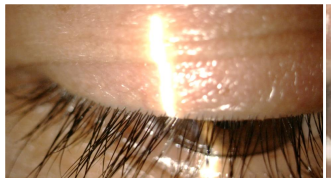
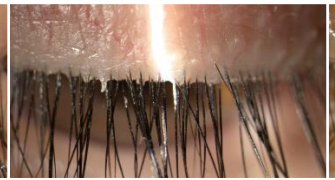
Assessing Severity of *Demodex* Blepharitis: Collarettes*

Collarette grade (nonlinear)				
0	1	2	3	4
				
0 to 2 lashes/eyelid with collarettes	3 to 10 lashes/eyelid with collarettes	>10 to <1/3 (~50)*,† lashes/eyelid with collarettes	≥1/3 to <2/3 (~100)*,† lashes/eyelid with collarettes	≥2/3 (~150)*,† lashes/eyelid with collarettes

*Per a randomized, controlled, double-masked, phase 2b/3 clinical trial of 421 patients with *Demodex* blepharitis.
†For an upper eyelid with 150 eyelashes (number of eyelashes on the upper eyelid may vary from 90 to 160).

Yeu E et al. *Cornea*. 2022. Ahead of print. doi:10.1097/ICO.0000000000003097

Assessing Severity of *Demodex* Blepharitis: Lid Erythema[1,*]

Grade 0	Grade 1	Grade 2	Grade 3
			
0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)

Images for Grades 0, 1, and 2 are from patients in the Saturn-1 trial. The image for Grade 3 has been reproduced with permission from Jiang et al.[2]

*Per the Saturn-1 trial. This was a randomized, controlled, double-masked, phase 2b/3 clinical trial of 421 patients with *Demodex* blepharitis.

1. You E et al. *Cornea*. 2022. Ahead of print. doi:10.1097/ICO.0000000000003097. 2. Jiang X et al. *Drug Des Dev Ther*. 2018 ;12:1269-1279.

Clinical Manifestations of *Demodex* Blepharitis

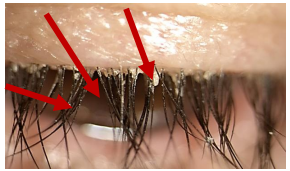


Image courtesy of Paul Karpecki, OD, FAAO, used with permission.[3]

Disorders of eyelashes[1,2]

Infestation of the lash follicles may lead to collarettes.

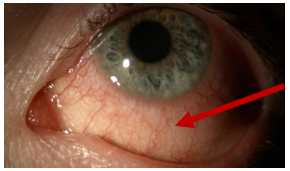


Image courtesy of Elise Kramer, OD, used with permission.[5]

Conjunctival inflammation[1,2]

Lid margin inflammation may spread over to the conjunctiva.

Image courtesy of Liu et al, used with permission.[1]

Lid margin inflammation[1,2]

Severe lid margin inflammation can be caused by mechanical blockage.

Image courtesy of Liu et al, used with permission.[1]

Corneal manifestations[1,2]

***D. brevis* is commonly associated with inflammation that spreads to the cornea, causing marginal infiltrates.**

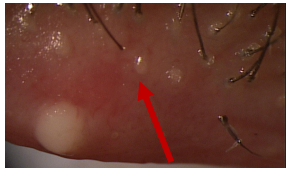


Image courtesy of Katherine Mastrota, MS, OD, EMBA, FAAO, used with permission.[4]

Meibomian gland dysfunction[1,2]

Blockage leads to filling, swelling, and many enlarged glands (cysts) or infection.

Image courtesy of Usiwoma Abugo, MD, used with permission.[6]

Chalazia[1,2]

The cytoskeleton of mites may act as a foreign body and create a granulomatous reaction that is implicated in chalazia.

1. Liu J et al. *Curr Opin Allergy Clin Immunol*. 2010;10(5):505-510. 2. Cheng AM et al. *Curr Opin Ophthalmol*. 2015;26(4):295-300. 3. Data on file. Image courtesy of Paul Karpecki, OD, FAAO; 2022. 4. Data on file. Image courtesy of Katherine Mastrota, MS, OD, EMBA, FAAO; 2022. 5. Data on file. Image courtesy of Elise Kramer, OD; 2022. 6. Data on file. Image courtesy of Usiwoma Abugo, MD; 2022.

Case: History

43 y.o. Caucasian Male
CC “here to have my chalazion removed – just moved to the area”
Recurrence x 3 over 4 years
Same location LUL

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Chronic Recurring Chalazion

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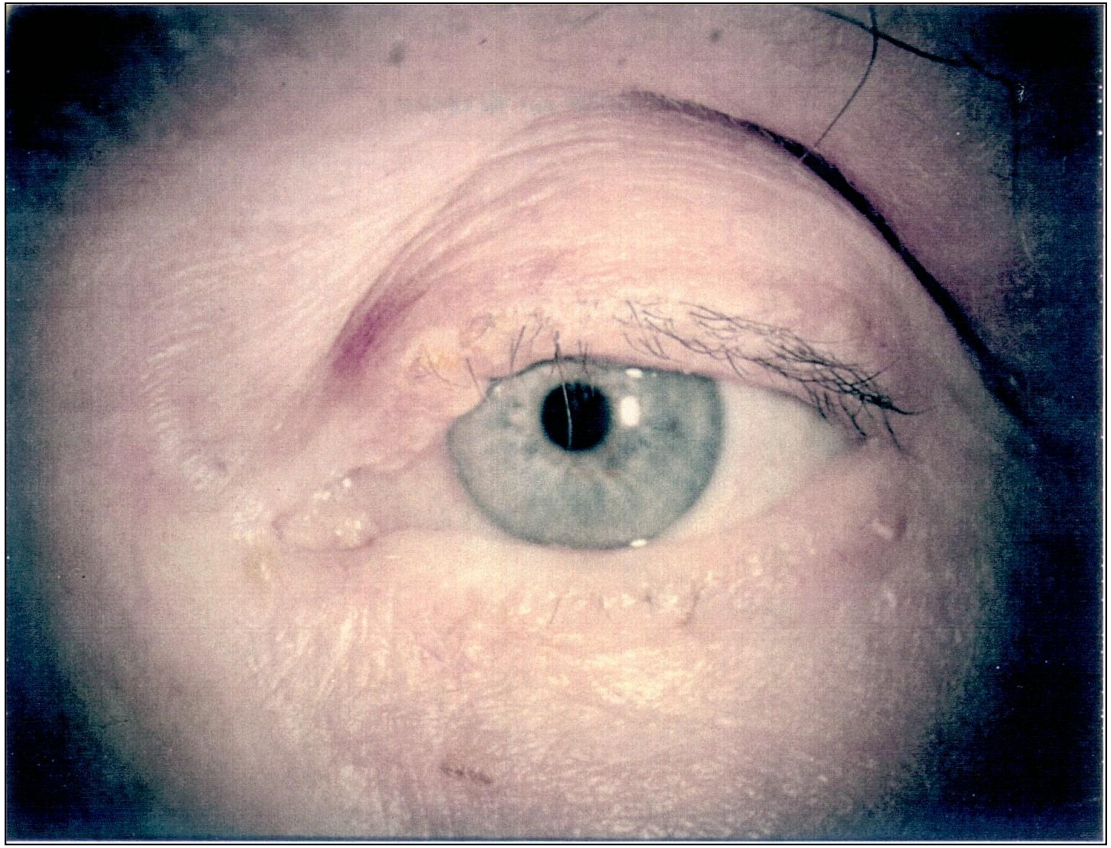

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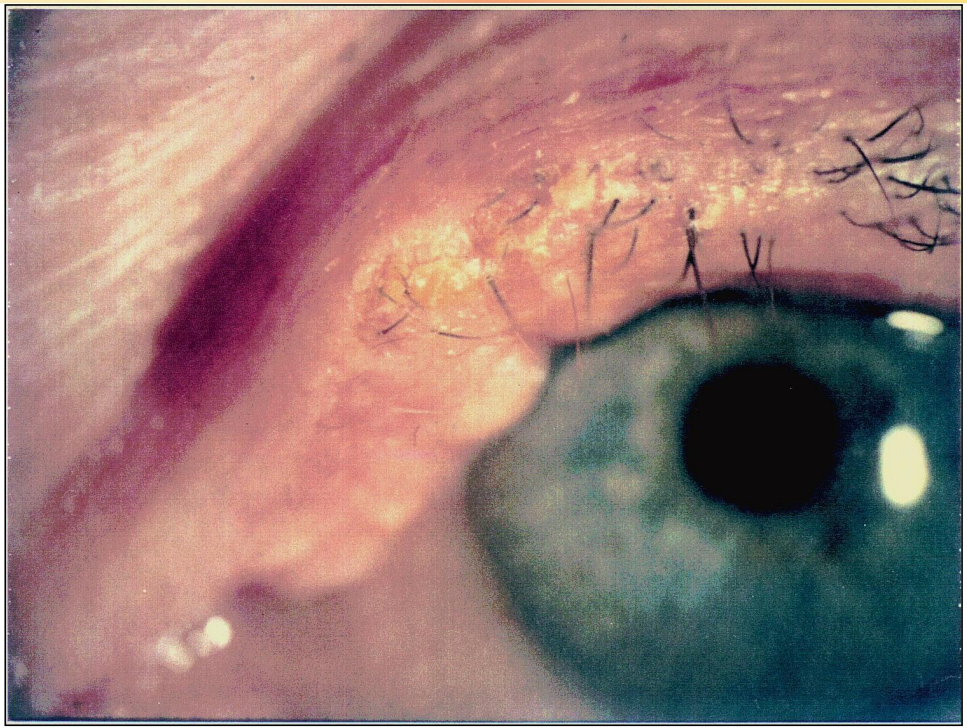

Sebaceous Carcinoma:

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Sebaceous Carcinomas

- Rare entity
- Usually originates from meibomian glands
- Can be highly malignant, infiltrative and metastasize
- Mortality may reach 30%
- May masquerade as a Chalazion - especially recurrent
- Watch for madarosis or displacement of normal tissue structure

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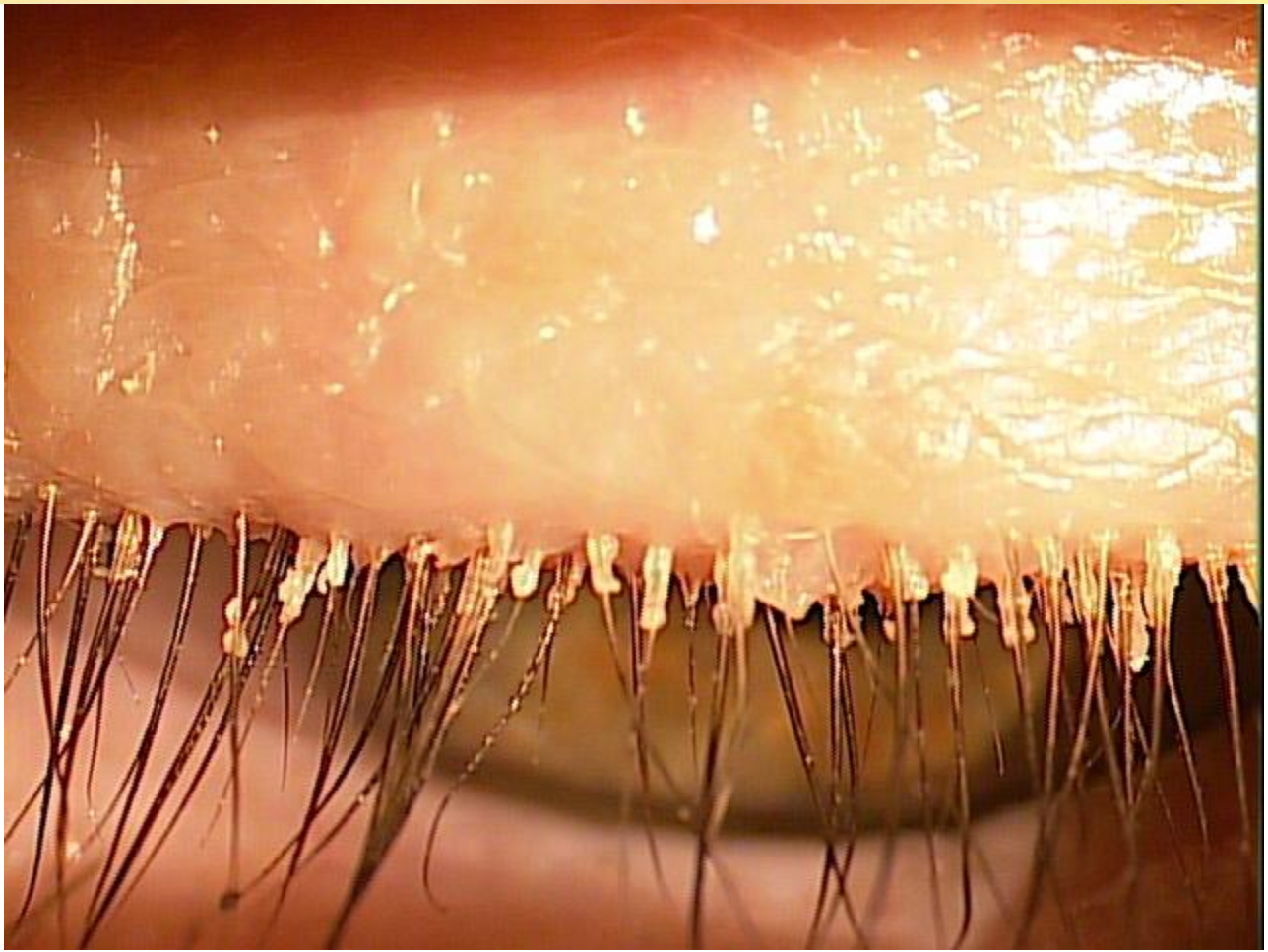

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What Are the Key Signs and Symptoms of *Demodex* Blepharitis?[1-4]

Signs and symptoms of DB

- Lid margin inflammation
- Dry eyes
- Itchy eyes
- Sensitivity to light
- Blurred vision
- Watering eyes
- Lid erythema
- Missing/misdirected lashes
- Contact lens intolerance
- Foreign body sensation

Collarettes are the pathognomonic sign of *Demodex* blepharitis

1. Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089-3094. 2. Kasetsuwan N et al. *Int J Ophthalmol.* 2017;10(1):122-127. 2. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 4. Mayo Clinic. Accessed September 13, 2022. https://www.mayoclinic.org/diseases-conditions/blepharitis/symptoms-causes/syc-20370141.

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Prevalence of *Demodex* Blepharitis

Up to 25 million individuals in the United States suffer from *Demodex* blepharitis.[1-3,*,†,‡]

~60% of patients visiting eye clinics each year have collarettes[3,4,‡]

- Collarettes are found in the eyelashes, whereas *Demodex* mites are found in the eyelash follicles[5,6]
- In 100% of lashes with collarettes, *Demodex* mites are found in follicles[5,6]

Prevalence of *Demodex* blepharitis[3,§]

- 69% of patients with blepharitis
- 60% of patients prescribed with dry eye disease medication
- 56% of cataract patients
- 51% of contact lens wearers

*Per a retrospective chart review of patients presenting with collarettes on clinical examination.
†Estimations per an analysis of US databases containing data on office-based eye care utilization.
‡Per a retrospective analysis of patients at 6 eye clinics who underwent slit lamp examination.
§As confirmed by the presence of collarettes.

1. Sadri E et al. Abstract presentation at: American Society of Cataract and Refractive Surgery Annual Meeting; July 24, 2021; Las Vegas, NV. Session SPS-107. 2. Wilson FA et al. *J Ophthalmol.* 2015;2015:435606. 3. Trattler W et al. *Clin Ophthalmol.* 2022;16:1153-1164. 4. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 5. Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089-3094. 6. Kasetsuwan N et al. *Int J Ophthalmol.* 2017;10(1):122-127.

Diagnosis and Prevalence Key Takeaways

- *Demodex* blepharitis is present in ~60% of all Americans visiting eye care providers (approximately 25 million people)[1-3]
- Collarettes are a pathognomonic sign of *Demodex* blepharitis[4,5]
- Checking for collarettes using a slit lamp should be part of every eye exam[1,4-6]
- All you need is a slit lamp and to have your patients look down[1,4-6]
- When you see collarettes, ask about irritation and lid hygiene[7,8]
- Symptoms such as itchy or dry eyes and lid margin inflammation are strong indicators of *Demodex* blepharitis[6,9]

1. Trattler W et al. *Clin Ophthalmol.* 2022;16:1153-1164. 2. Sadri E et al. Abstract presentation at: American Society of Cataract and Refractive Surgery Annual Meeting; July 24, 2021; Las Vegas, NV. Session SPS-107. 3. Wilson FA et al. *J Ophthalmol.* 2015;2015:435606. 4. Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9);3089-3094. 5. Katsetuwan N et al. *Int J Ophthalmol.* 2017;10(1):122-127. 6. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 7. Zhang AC et al. *Ophthalmic Physiol Opt.* 2020;40(4):389-432. 8. Hosseini K et al. *Health Qual Life Outcomes.* 2018;16(1):11. 9. Mayo Clinic. Accessed September 13, 2022. https://www.mayoclinic.org/diseases-conditions/blepharitis/symptoms-causes/syc-20370141

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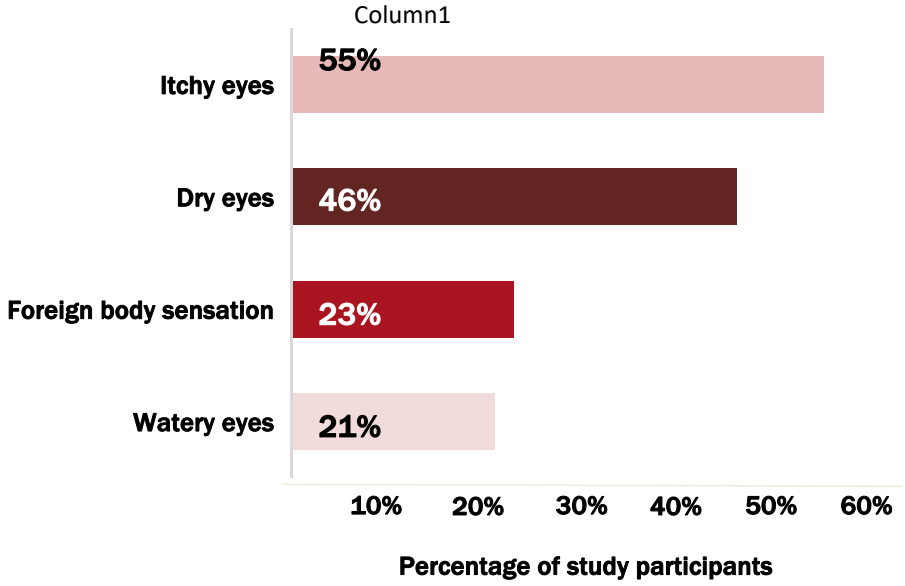
Clinical and Psychosocial Burden of *Demodex* Blepharitis*

Bothersome symptoms reported by patients

- Itchy eyes
- Dry eyes
- Foreign body sensation
- Watery eyes
- Crusty eyes
- Blurred vision

Frequency of bothersome symptoms



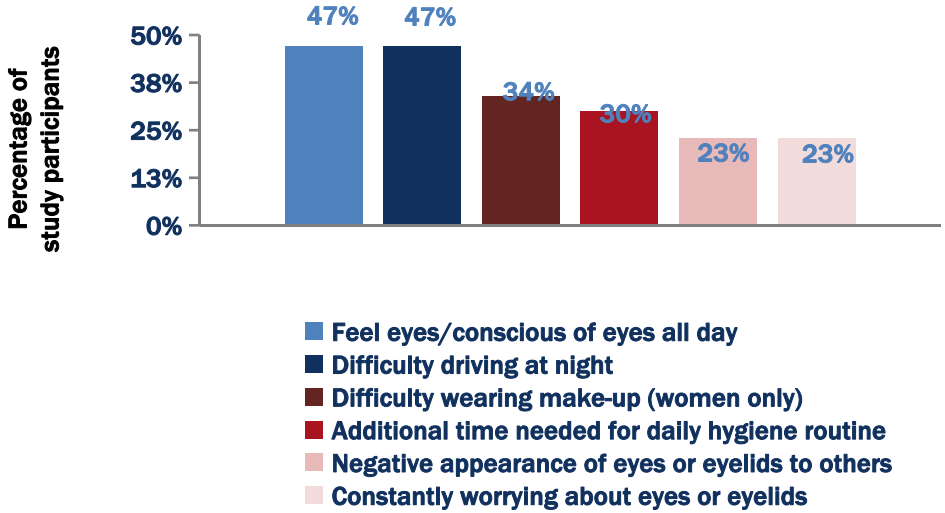
*Per the Atlas study (an observational study of 311 adult *Demodex* blepharitis patients from 8 US ophthalmic and optometric centers). This study was funded by Tarsus Pharmaceuticals.

O'Dell L et al. *Clin Ophthalmol*. 2022;16:2979-2987.

Symptom Duration and Impact on Quality of Life

- 51% of patients experienced signs and symptoms > 4 years
- 58% of patients were never diagnosed with blepharitis
- 33% of patients made at least 2, and sometimes >6, visits to a doctor for this condition

Impact of *Demodex* blepharitis symptoms on daily life



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Common Concomitant Disorders in Patients With *Demodex* Blepharitis

Demodex blepharitis is prevalent in patients receiving eye exams, regardless of the reason for the eye care visit.[1,2]

The prevalence of *Demodex* blepharitis for patients presenting with:

- Dry eye disease (n=593)[1]: 59%
- Glaucoma (n=236)[1]: 65%
- Contact lens wearers (n=87)[1]: 51%
- Meibomian gland dysfunction (n=211)[1]: 57%
- All patients (6 eye care centers; n=1032)[1,*]: 58%

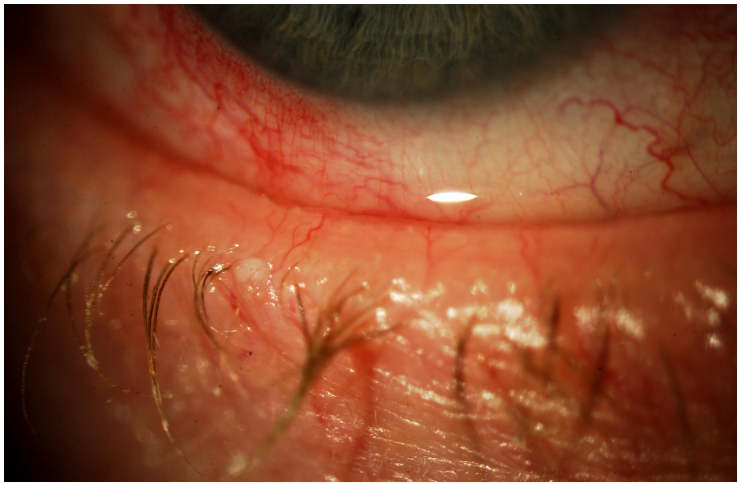
*Per an IRB-approved retrospective chart review of patients examined for collarettes across 6 US eye care clinics seen for annual examination, cataracts, dry eye disease, and/or glaucoma.
IRB, institutional review board.

1. Trattler W et al. *Clin Ophthalmol.* 2022;16:1153-1164. 2. Wesolowska M et al. *Arch Med Sci.* 2014;10(2):319-324.

Rosacea and *Demodex* Blepharitis

Searching for *Demodex* infestation in the eyelash follicles of patients diagnosed with rosacea can impact management and potentially modify the course of disease.[1,2]

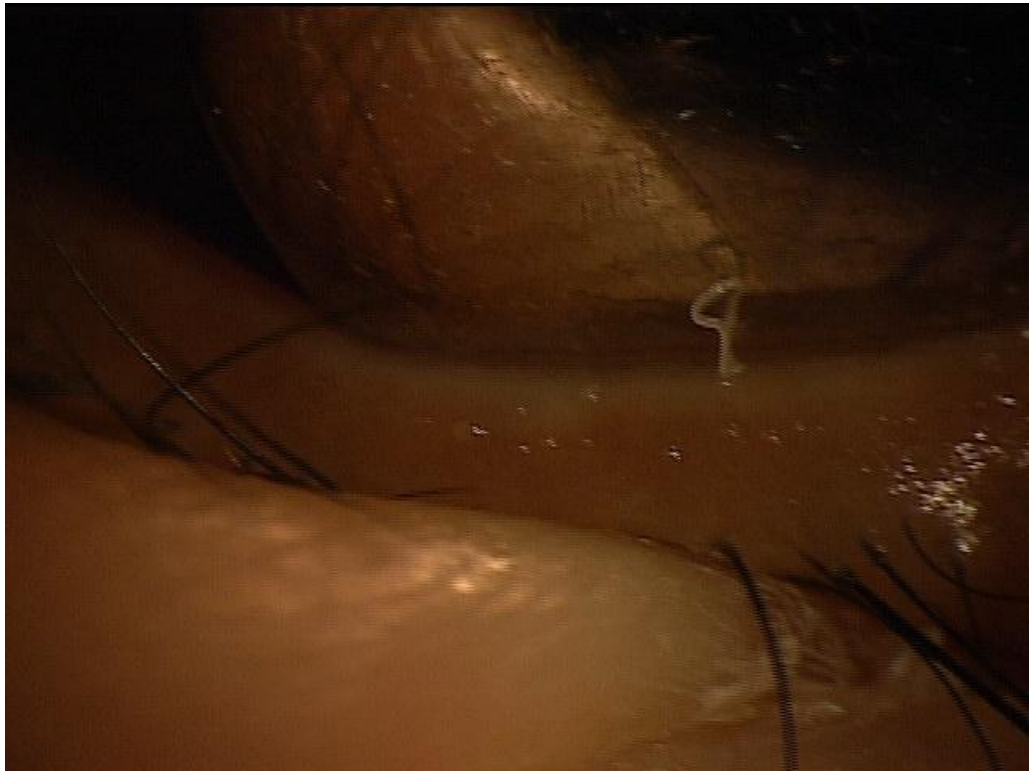
- The pathophysiology of rosacea is complex and multifactorial, and the host's immunological interactions with *Demodex* mites are not fully understood[1]
- Factors such as immunosuppression, diabetes, and sebaceous hyperplasia may contribute to increased *Demodex* proliferation—a contributor of inflammatory responses associated with rosacea[1]
- 59% of patients presenting with facial rosacea have *Demodex* infestation[2,*]



*Per a cross-sectional analysis of 82 patients, where slit lamp examination was used to identify collarettes and eyelid margin telangiectasia.

1. Forton FMN et al. *Dermatol Ther (Heidelb).* 2020;10(6):1229-1253. 2. Gonzalez-Hinojosa D et al. *Indian J Ophthalmol.* 2018;66(1):36-38. 3. Data on file. Image courtesy of Scheffer Tseng, MD, PhD; 2022.

MGD/EDED and *Demodex* Blepharitis



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ILS and *Demodex* Blepharitis

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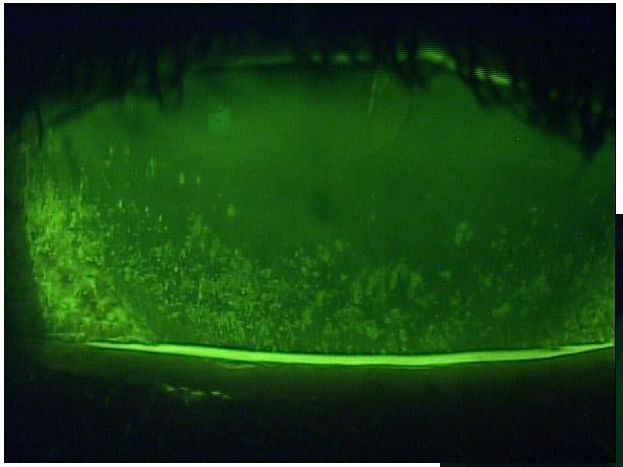
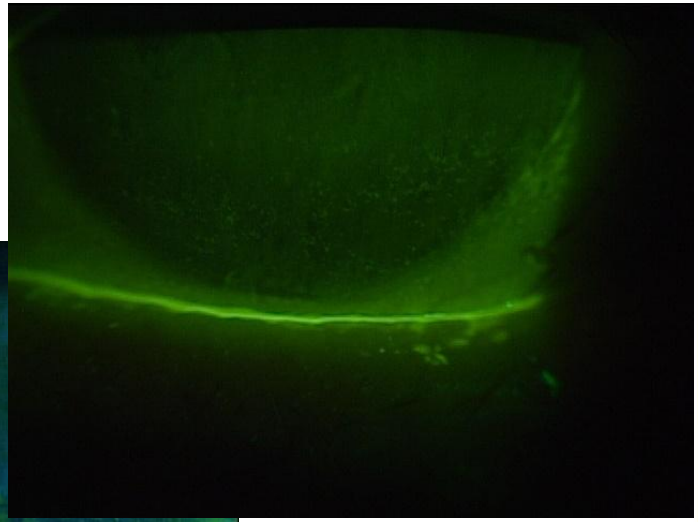
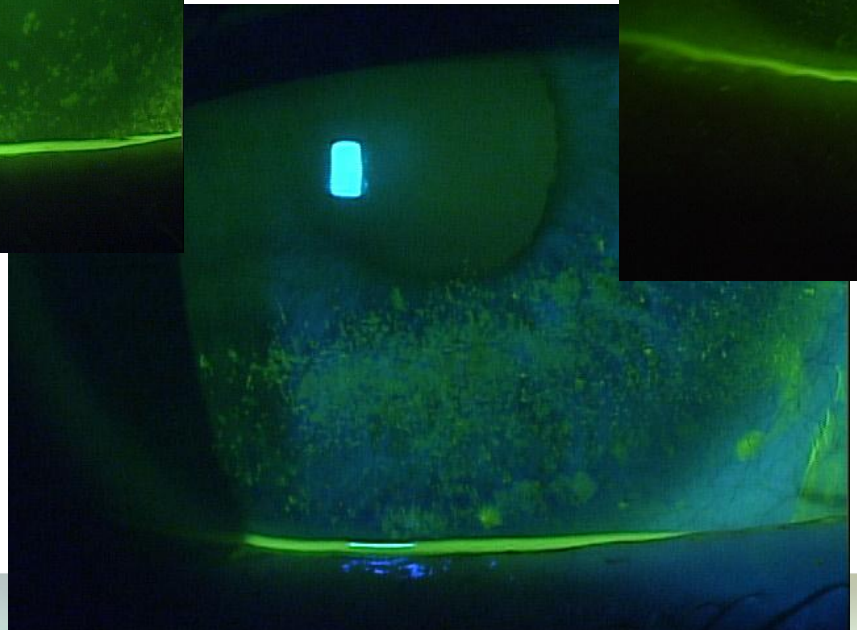
ILS and *Demodex* Blepharitis







Key Takeaways

- *Demodex* blepharitis is common in patients with ocular surface diseases and contact lens wearers[1,2]
- *Demodex* infestation can lead to dermatological conditions such as rosacea[3,4]
- *Demodex* is also highly associated with MGD/EDE and ILS

1. Trattler W et al. *Clin Ophthalmol.* 2022;16:1153-1164. 2. Wesolowska M et al. *Arch Med Sci.* 2014;10(2):319-324. 3. Forton FMN et al. *Dermatol Ther (Heidelb).* 2020;10(6):1229-1253. 4. Gonzalez-Hinojosa D et al. *Indian J Ophthalmol.* 2018;66(1):36-38.

Overview of Discussion

I: *Demodex* Blepharitis: An Introduction

II: Diagnosis and Prevalence

III: Clinical and Psychosocial Burden of *Demodex* Blepharitis

IV: Concomitant Disorders

V: Case Studies

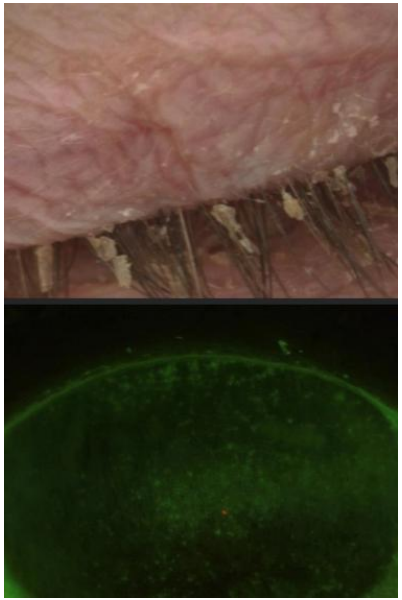
VI: Current and Emerging Management Approaches

PK

Case 1*

Patient history

A woman suffering from “chronic blepharitis for a lifetime” had previously visited several eye care professionals and complained of “greasy yellow debris” below her eyelids. She had undergone prior lid surgery, and had been on several medications for dry eye disease



Examination findings

Diagnosed with dry eye disease along with longstanding corneal pannus; osmolarity was normal

Management

Lid scrubs and antibiotics prescribed with the assumption that she was suffering from staphylococcus blepharitis only provided temporary relief

- During her follow-up visit, the doctor prescribed a different combination of antibiotics

Conclusion

The online forum discussions focused on antibiotic therapies and palliative care rather than checking for *Demodex* infestation

*Patient details and images were obtained from an online eye care forum that was shared for discussion.

PK

Case 2*

Patient history

A man with normal bloodwork and no underlying health conditions presented with yellowish debris on lower lids that kept coming back

- The patient was known to maintain good personal hygiene, such as changing pillowcases every day

Management

The patient attempted many different treatments, including a 50% tea tree oil soak, lid scrubs, dry eye medication, an antibiotics regimen, and multiple rounds of radiofrequency and intense pulsed light treatments over several months

- None of these therapies provided relief or improved the clinical appearance of eyelids

Conclusion

Despite months of suffering, the doctor never considered checking for *Demodex* infestation

*Patient details and images were obtained from an online eye care forum that was shared for discussion.

PK

Case 3*

Patient history

A 26-year-old, healthy, female patient presented with itchy eyelids, red and irritated eyes, mild ocular rosacea, and obstructive meibomian gland dysfunction

- Her symptoms began 2 years ago following a hair dye treatment

Management

Despite testing negative for chemical allergies, she underwent treatment for contact dermatitis. This did not resolve her itchy, inflamed eyelids

- Intense pulsed light treatment provided only temporary relief of disease-related symptoms
- Doctor recommended using cold packs instead of warm compresses at home

Conclusion

The doctor never considered checking for *Demodex* mites despite clear symptoms and prior diagnosis of obstructive meibomian gland dysfunction

*Patient details and images were obtained from an online eye care forum that was shared for discussion.

PK

Key Takeaways

- *Demodex* blepharitis is routinely misdiagnosed or missed by eye care professionals

- When patients presenting with “yellow debris” on their eyelashes only get temporary relief from antibiotics and palliative measures, check for collarettes

PK

Overview of Discussion

I: *Demodex* Blepharitis: An Introduction

II: Diagnosis and Prevalence

III: Clinical and Psychosocial Burden of *Demodex* Blepharitis

IV: Concomitant Disorders

V: Case Studies

VI: Current and Emerging Management Approaches

SG

Current Management Strategies

- The first and only treatment for *Demodex* blepharitis was very recently approved: **Lotilaner 0.25% ophthalmic solution**
- Dosing igtt BID x 6 weeks OU
- Rub Excess into lashes, around face

FDA, US Food and Drug Administration.

1. Shah PP et al. *Cornea*. 2022;41(8):934-939. 2. Zhang AC et al. *Ophthalmic Physiol Opt*. 2020;40(4):389-432.

SG

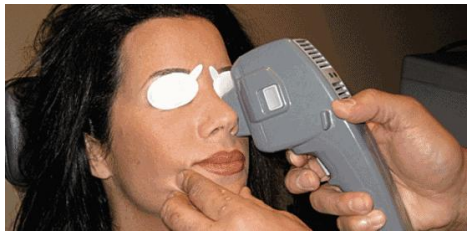
Current Management Approaches[1]

At-home options:

- Tea tree oil
- Antibiotics
  - Ointment (erythromycin)
  - Oral (metronidazole)
- Manuka honey/coconut oil/aloe vera
- Lid wipes

In-office options:

- Intense pulsed light therapy (IPL)
- Low level light therapy (LLLT)
- Microblepharoexfoliation



Images courtesy of Katherine Mastrota, MS, OD, EMBA, FAAO, used with permission.[2]

*No peer-reviewed evidence available for *Demodex* eradication.
IPL, intense pulsed light therapy; T4O, terpinen-4-ol.

1. Huo Y et al. *Ann Transl Med*. 2021;9(3):238. 2. Data on file. Images courtesy of Katherine Mastrota, MS, OD, EMBA, FAAO; 2022.

SG

Tea Tree Oil (TTO)

- **Essential oil composed of monoterpenes derived from the leaves of *Melaleuca alternifolia*[1]**
- **Active ingredient: terpinen-4-ol (T40)**
  - Anti-inflammatory, antimicrobial, and antifungal properties
  - Concentrations 5 to 50%
  - OTC lid wipes not as potent in killing *Demodex* as 50% formulation[2]
- Strong menthol-like sensation/stinging

*No peer-reviewed evidence available for *Demodex* eradication.
OTC, over the counter; T40, terpinen-4-ol; TTO, tea tree oil.

1. Hunyh Q et al. *J Phys Conf Ser.* 2012;352;012053. 2. Cheung IMY et al. *Cont Lens Anterior Eye.* 2018;41(6):513-517.

SG

Evaluation of the Efficacy of Tea Tree Oil On the Density of *Demodex* Mites (Acari: Demodicidae) and Ocular Symptoms In Patients With Demodectic Blepharitis

Authors: Yücel Karakurt and Erhan Zeytun
Source: Journal of Parasitology, 104(5):473-478

Published By: American Society of Parasitologists URL: https://doi.org/10.1645/18-46	% Patients with *Demodex*		Conclusions
	Baseline	Post-treatment	
7.5% TTO eyelash shampoo Twice a day for 4 weeks (N=75)	100%	64% (36.0% patients with mite eradication)	• Full *Demodex* reduction was attained in 36% in TTO group and 11.7% in the control group post-treatment • The mean collarettes grade were reduced significantly in the TTO group compared to the control group ($p<0.001$*)
TTO-free eyelash shampoo Twice a day for 4 weeks (N=75)	100%	88.3% (11.7% patients with mite eradication)	

TTO, tea tree oil.

Karakurt Y and Zeytun E. *J Parasitol*. 2018;104(5):473-478.

SG

Double-Masked and Unmasked Prospective Study of Terpinen-4-ol Lid Scrubs With Microblepharoexfoliation for the Treatment of *Demodex* Blepharitis

Ilan J. Epstein, MD, Eric Rosenberg, DO, Ross Stuber, BA, Michael B. Choi, MD, Eric D. Donnenfeld, MD, and Henry D. Perry, MD

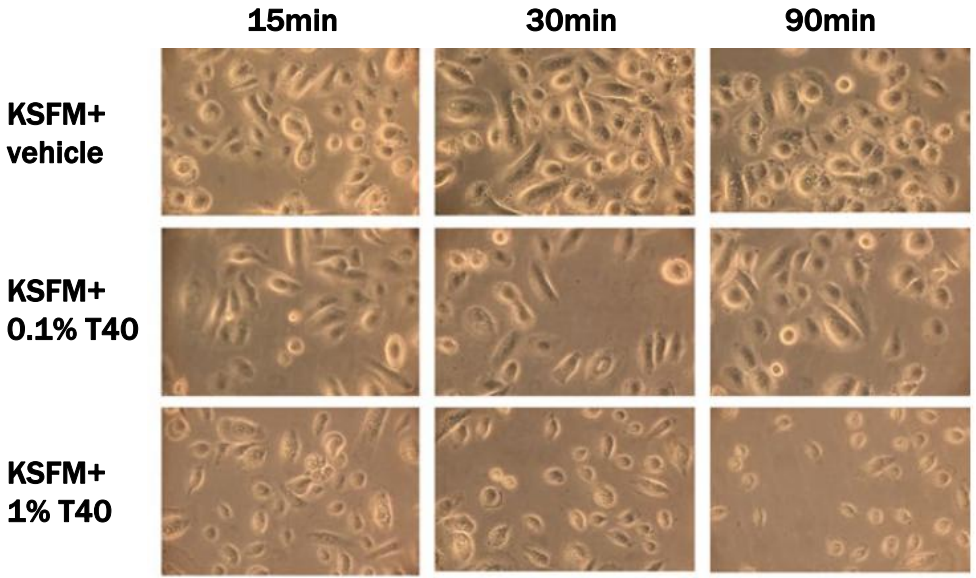
Approach (N)	Total *Demodex* Count (per 4 lashes)		Conclusions
	Baseline	Post-treatment	
Terpinen-4-ol lid scrubs twice daily for 30 days + MBE on days 1 and 30 (N=23)	4.7	3.6	No differences were observed in *Demodex* counts between in-office MBE combined with either terpinen-4-ol lid scrubs or sham scrubs (p>0.05)
Sham scrubs twice daily for 30 days + MBE on days 1 and 30 (N=23)	5.1	3.0	

MBE, microblepharoexfoliation.

Epstein IJ, et al. *Cornea*. 2020;39(4):408-416.

SG

Tea Tree Oil (TTO)



Images courtesy of Chen et al, used with permission.

KSFM, keratinocyte serum free media; T40, terpinen-4-ol.

Effects of Terpinen-4-ol on meibomian gland epithelial cells *in vitro*

Di Chen, MD[1,2], Jingyi Wang, MD[1,2], David A. Sullivan, MS, PhD, FARVO[2], Wendy R. Kam, MS[2], Yang Liu, MD[2]

- After 15 minutes of exposure to 1% T40, immortalized human meibomian gland epithelial cells exhibited rounding, atrophy, and poor adherence
- Within 90 minutes of such treatment, almost all cells were detached, floating in the medium, and dead

Chen D et al. *Cornea*. 2020;39(12):1541-1546.

SG

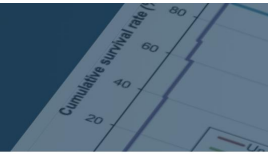
Manuka honey/coconut oil/aloe vera

FULL LENGTH ARTICLE | VOLUME 41, ISSUE 6, P527-530, DECEMBER 01, 2018

Comparing the *in vitro* effects of MGO™ Manuka honey and tea tree oil on ocular *Demodex* viability

Katie Frame • Isabella M.Y. Cheung • Michael T.M. Wang • Philip R. Turnbull • Grant A. Watters • Jennifer P. Craig

Published: July 06, 2018 • DOI: https://doi.org/10.1016/j.clae.2018.06.006 • Check for updates



Highlights

- *In vitro* anti-parasitic efficacy study of 52 *Demodex* mites.
- Mites were randomised to cyclodextrin-complexed and uncomplexed Manuka honey, tea tree oil, or no treatment application.
- Mite viability was assessed for 240 min following treatment application.
- Cyclodextrin-complexed Manuka honey demonstrated comparable anti-demodectic efficacy to 50% tea tree oil (TTO).
- Complexed honey with proven *in vivo* tolerability shows promise as possible alternative to TTO for demodex eradication.

Abstract

Purpose

To compare the *in vitro* antiparasitic effects of MGO™ Manuka honey and tea tree oil against ocular *Demodex*.

Methods

Fifty-two viable *Demodex* mites were acquired from the epilated eyelashes of 9 participants with blepharitis and symptomatic dry eye. Viable mites were randomised to one of five treatment groups: cyclodextrin-complexed and uncomplexed Manuka Honey, 100% and 50% tea tree oil, and no treatment. Following treatment application, mite viability was assessed for 240 min, based on limb and body movement and/or the development of a crenated/translucent appearance. Kaplan-Meier survival analysis was then performed.

Results

The log-rank test demonstrated a significant treatment effect on the survival distribution of *Demodex* mites ($p < 0.001$). Bonferroni-corrected post-hoc pairwise analysis showed that all treatments except for uncomplexed honey effected lower survival probabilities than the untreated group (all $p < 0.001$). Among the four treatments, survival probabilities were lowest with 100% tea tree oil (all $p < 0.001$), and highest with uncomplexed honey (all $p \leq 0.001$). No difference was observed between complexed honey and 50% tea tree oil ($p = 0.81$).

Conclusions

The *in vitro* efficacy of cyclodextrin-complexed Manuka honey was comparable with 50% tea tree oil, an established treatment for ocular *Demodex*. The findings support future clinical trials investigating the therapeutic effects of complexed honey in demodectic blepharitis patients.

SG

Manuka honey/coconut oil/aloe vera

Original Research Article

Role of demodex infestation in blepharitis and coconut oil as a treatment option

Suresha A R[1], Sadhwini M H[1,*]

[1] *Dept. of Ophthalmology, JJM Medical College, Davangere, Karnataka, India*

ARTICLE INFO

Article history:
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Keywords:
Anterior blepharitis
Demodex infestation
Meibomian gland dysfunction
Non-specific irritation

ABSTRACT

Purpose: To assess incidence of demodex species, correlate ocular symptomatology, evaluate efficacy of coconut oil as treatment method in all types of blepharitis.
Materials and Methods: 30 patients with anterior & mixed blepharitis, meibomian gland dysfunction & non-specific irritation were enrolled for study. History taken & examined clinically. 2 lashes/lid were sampled & mounted on slides with normal saline & observed under light microscope. Number of mites counted. Patients positive for demodex were treated with coconut oil application over lid margins & reviewed after 3 weeks.
Results: Incidence of demodex was 40% & it increased with age. Demodex was commonly associated with meibomian gland dysfunction, non-specific irritation, madarosis, cloudy & toothpaste like meibum quality. Burning sensation and itching were common complaints. At 3rd week, all patients were symptom-free. Mite count dropped by 52.8% but were not eliminated.
Conclusion: Demodex infestation is often overlooked but it is associated with about half of blepharitis cases. Hence further evaluation should be considered. Coconut oil is an easily available mode of treatment & helps reduce symptoms and mite counts.

SG

Manuka honey/coconut oil/aloe vera

ALOE VERA: A SHORT REVIEW

Amar Surjushe, Resham Vasani, and D G Saple

Abstract Go to:

Aloe vera is a natural product that is now a day frequently used in the field of cosmetology. Though there are various indications for its use, controlled trials are needed to determine its real efficacy. The aloe vera plant, its properties, mechanism of action and clinical uses are briefly reviewed in this article.

***Healing properties*:** Glucomannan, a mannose-rich polysaccharide, and gibberellin, a growth hormone, interacts with growth factor receptors on the fibroblast, thereby stimulating its activity and proliferation, which in turn significantly increases collagen synthesis after topical and oral Aloe vera.[9] Aloe gel not only increased collagen content of the wound but also changed collagen composition (more type III) and increased the degree of collagen cross linking. Due to this, it accelerated wound contraction and increased the breaking strength of resulting scar tissue.[10] An increased synthesis of hyaluronic acid and dermatan sulfate in the granulation tissue of a healing wound following oral or topical treatment has been reported.[11]

Anti-inflammatory action: Aloe vera inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Recently, the novel anti-inflammatory compound called C-glucosyl chromone was isolated from gel extracts.[8]

Antiviral and antitumor activity: These actions may be due to indirect or direct effects. Indirect effect is due to stimulation of the immune system and direct effect is due to anthraquinones. The anthraquinone aloin inactivates various enveloped viruses such as herpes simplex, varicella zoster and influenza.[18] In recent studies, a polysaccharide fraction has shown to inhibit the binding of benzopyrene to primary rat hepatocytes, thereby preventing the formation of potentially cancer-initiating benzopyrene-DNA adducts. An induction of glutathione S-transferase and an inhibition of the tumor-promoting effects of phorbol myristic acetate has also been reported which suggest a possible benefit of using aloe gel in cancer chemoprevention.[19,20]

Moisturizing and anti-aging effect: Mucopolysaccharides help in binding moisture into the skin. Aloe stimulates fibroblast which produces the collagen and elastin fibers making the skin more elastic and less wrinkled. It also has cohesive effects on the superficial flaking epidermal cells by sticking them together, which softens the skin. The amino acids also soften hardened skin cells and zinc acts as an astringent to tighten pores. Its moisturizing effects has also been studied in treatment of dry skin associated with occupational exposure where aloe vera gel gloves improved the skin integrity, decreases appearance of fine wrinkle and decreases erythema.[21] It also has anti-acne effect.

Antiseptic effect: Aloe vera contains 6 antiseptic agents: Lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols and sulfur. They all have inhibitory action on fungi, bacteria and viruses.

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Current Eye Research

Therapeutic Effects of Intense Pulsed Light on Ocular Demodicosis

XiaoZhao Zhang, Nan Song and Lan Gong
ISSN: 0271-3683 (print) 1460-2022 (Online) Journal homepage: https://www.tandfonline.com/loi/icey20

Approach (N)	*Demodex* Counts (mean mite count/8 lashes)		Conclusions
	Baseline	Post-treatment	
IPL 3x treatments* within 90 days (N=20)	13.05	−13.05	No differences were observed in *Demodex* counts in the two groups after 90 days of treatment (p>0.05)
5% TTO daily for 90 days (N=20)	12.85	−11.05	

*Only administered to skin type 4 or less patients.
IPL, intense pulsed light; TTO, tea tree oil.

Zhang X et al. *Curr Eye Res.* 2019;44(3):250-256.

SG

Efficacy of Topical Ivermectin 1% in the Treatment of *Demodex* Blepharitis

Young Choi, MD, Youngsub Eom, MD, PhD, Eun Gyu Yoon, MD, Jong Suk Song, MD, PhD, Il-Hwan Kim, MD, PhD, and Hyo Myung Kim, MD, PhD

Approach (N)	Collarette Grade (0-4 point scale)		Conclusions
	Baseline	Post-treatment	
Ivermectin 1% cream once weekly + daily TTO eyelid hygiene for 15 weeks (N=51)	2.2	1.1	The mean collarettes grade of the ivermectin group was significantly less than that of the control group after the follow-up of 15 weeks (p<0.001)
Daily TTO eyelid hygiene for 15 weeks (N=51)	2.0	1.6	

TTO, tea tree oil.

Choi Y et al. *Cornea*. 2022;41(4):427-434.

SG

ACTA SCIENTIFIC OPHTHALMOLOGY (ISSN: 2582-3191)
Volume 3 Issue 9 September 2020
Research Article

Lid Hygiene Versus Lid Hygiene Plus Microblepharoexfoliation for the Treatment of *Demodex folliculorum* Blepharitis

Michael B. Choi and Rebecca Stein

Approach (N)	Total *Demodex* Count (per 4 lashes)		Conclusions
	Baseline	Post-treatment	
In-office MBE + lid hygiene with warm compresses twice a day for 1 month (N=24)	5.32	−3.88	Patients receiving MBE showed a statistically greater decrease in the *Demodex* counts than those receiving lid hygiene alone (p<0.001)
Lid hygiene with warm compresses twice a day for 1 month (N=22)	4.08	−0.04	

MBE, microblepharoexfoliation.

SG

Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of *Demodex folliculorum*

Doaa Abdel-Badie Salem, Atef El-Shazly, Nairmen Nabih, Youssef El-Bayoumy, Sameh Saleh

Approach (N)	Total *Demodex* Count (per 3 lashes)		Conclusions
	Baseline	Post-treatment	
Metronidazole (250 mg three times per day for 2 weeks) and ivermectin (two doses of 200 mg/kg, 1 week apart) (N=15)	15	0.2	Combined therapy was superior in decreasing the *Demodex* counts compared to ivermectin alone ($p<0.001$)
Ivermectin alone (two doses of 200 mg/kg, 1 week apart) (N=15)	12.8	5.3	

Salem DA et al. *Int J Infect Dis*. 2013;17(5):343-734.

SG

Lotilaner Ophthalmic Solution, 0.25%

TP-03 (lotilaner ophthalmic solution, 0.25%) was FDA approved for the Treatment of Demodex Blepharitis: August 2023

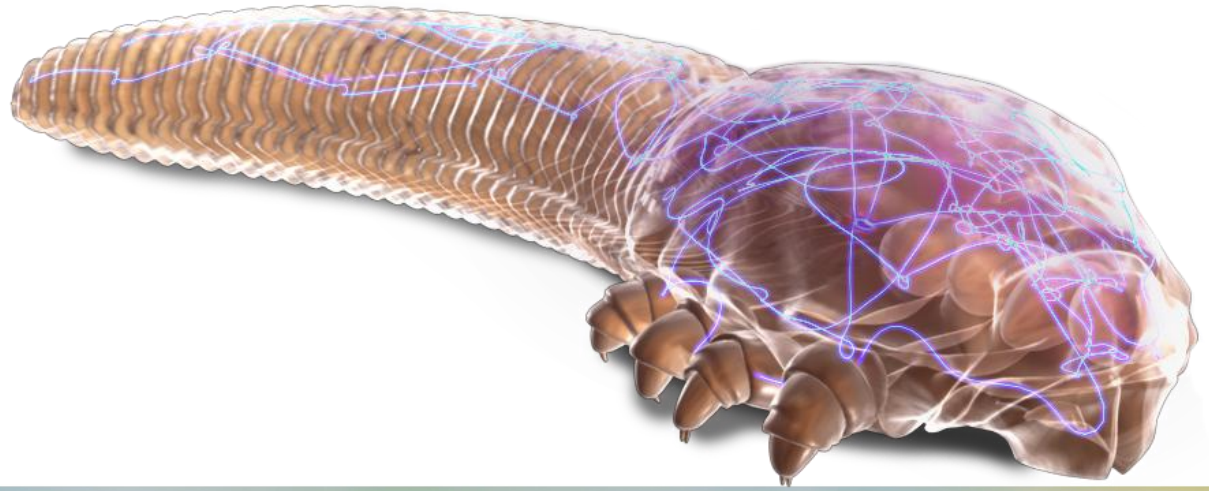
- Ophthalmic topical eye drop, preserved in bottle
- Lipophilic: potentially enables it to flow into the lash follicle
- BID doxing x 6 weeks
- Oral lotilaner: approved commercially for treating fleas and ticks in cats and dogs
    - Used off-label for *Demodex* infestations in animals
- Mechanism of action: non-competitive antagonist of parasitic gamma-aminobutyric acid-gated chloride channels
    - Causes paralysis and death of *Demodex* mites

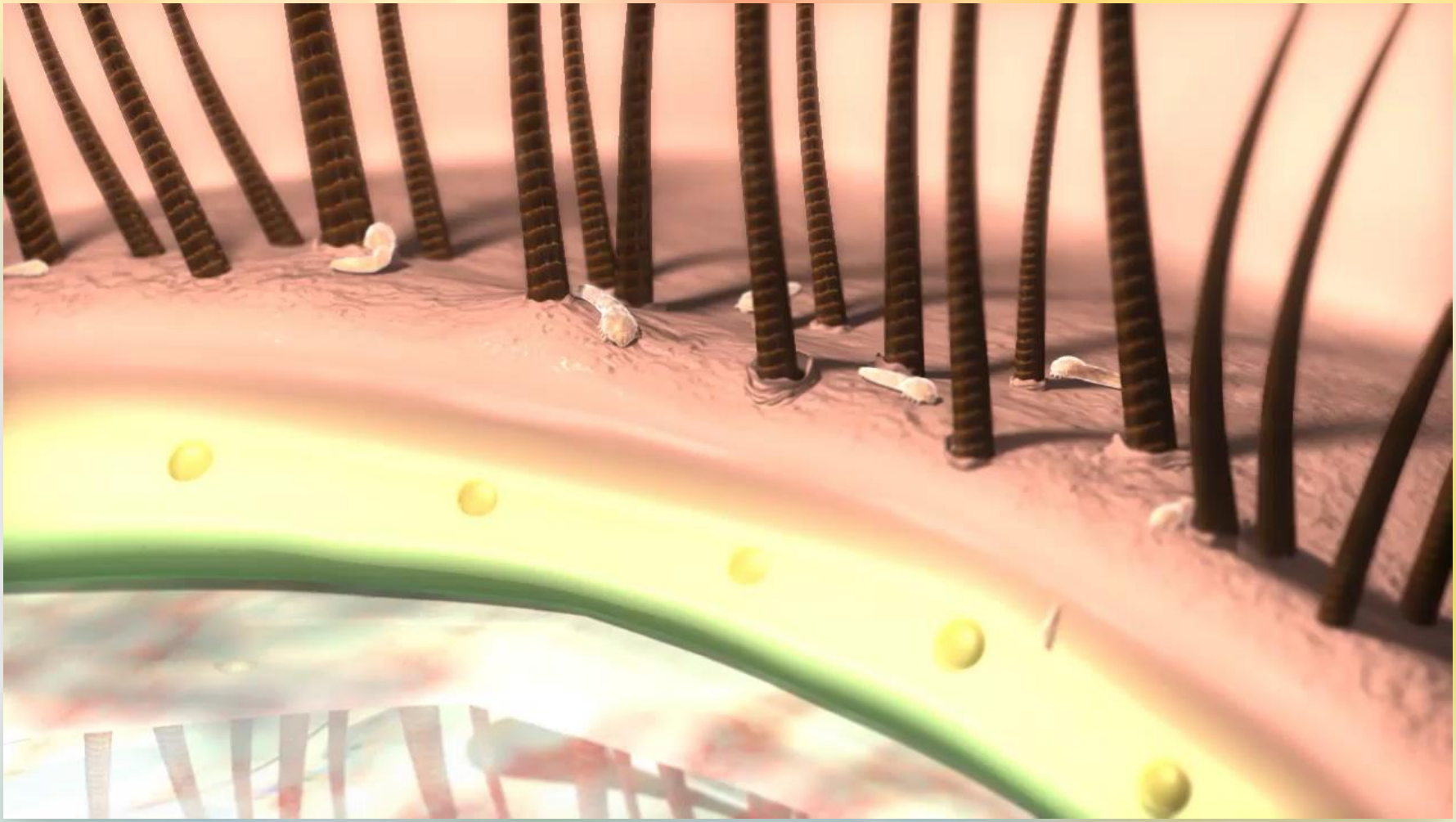
FDA, US Food and Drug Administration; NDA, New Drug Application.

SG

Lotilaner 0.25% is a First in Class Novel Drug Designed to Eradicate Demodex Mites and Treat Blepharitis

Designed to paralyze the mite nervous system through parasite-specific GABA inhibition



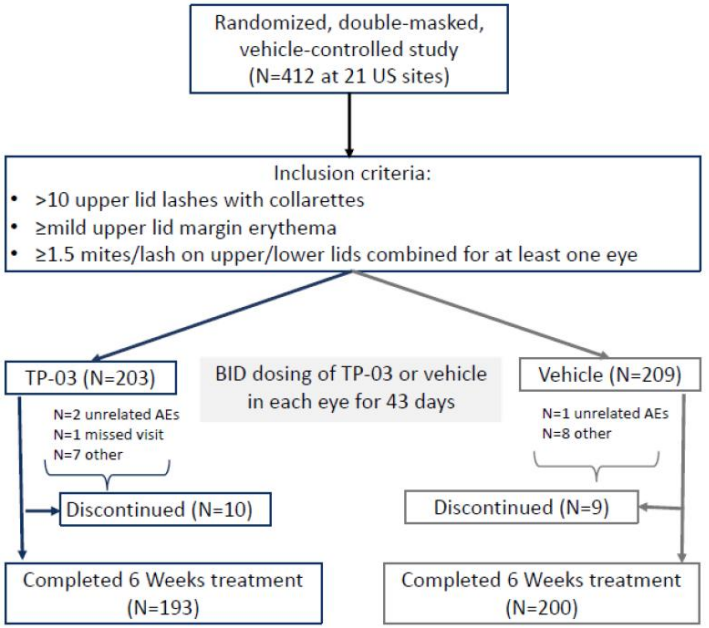


Cure of Collarettes with BID Use of Lotilaner

Safety & Efficacy of Lotilaner Ophthalmic Solution, 0.25% in Treating *Demodex* Blepharitis: Results of the Phase III Saturn-2 Trial

Paul Karpecki, OD[1,2]; Patrick Vollmer, OD[1,3]; Scott Schecter, OD[1,4]; Jared Peterson, MD[1,5]; Gregg Berdy, MD[1,6]; Michael Samuels, OD[1,7]; Blake Simmons, OD[1-8]; Mark Holdbrook[9]; Stephanie Baba, OD[9]; John Meyer, MD[1,10]

Disclosures: [1]Consultant for Tarsus Pharmaceuticals, Inc., Irvine, CA; [2]Kentucky Eye Institute, Louisville, KY; [3]Vita Eye Clinic, Shelby, NC; [4]Rainbow Eye Center, Miami, FL; [5]Mountain View Eye Center, Layton, UT; [6]Ophthalmology Associates, St Louis, MO; [7]NC Eye Associates, Apex, NC; [8]Vision Institute, Colorado Springs, CO; [9]Employee of Tarsus Pharmaceuticals, Inc., CA; [10]The Eye Care Institute, Louisville, KY



AE, adverse event; BID, twice daily; TP-03, lotilaner ophthalmic solution, 0.25%; US, United States.

Karpecki P et al. Abstract presented at: American Academy of Optometry Annual Meeting. October 2022; San Diego, CA.

SG

Pivotal Trial Results: Saturn 1 and 2[1,2]

- Patients diagnosed with collarettes
- Dosing BID for 6 weeks

Combined Pivotal Data (N=833) at Week 6 (TP-03 vs vehicle)	
Primary Endpoint: Complete Collarette Cure (Grade 0)	50% vs 10%
Clinically Meaningful Collarette Cure* (Grade 0 or 1)	85% vs 28%
Secondary Endpoint: Mite Eradication	60% vs 16%
Lid Erythema Cure	25% vs 8%
Safety	Generally safe and well tolerated

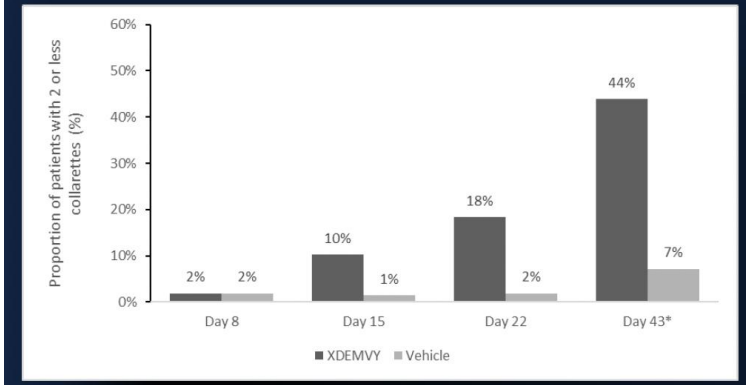
*As a measure of diminished chances of infestation.
BID, twice daily; TP-03, lotilaner ophthalmic solution, 0.25%.

1. Yeu E et al. Abstract presented at: American Academy of Ophthalmology Annual Meeting. September 2022; Chicago, IL. Session ID P0058. 2. Yeu E et al. *Cornea*. 2022;10.1097/ICO.0000000000003097.

SG

Figure 1. Saturn-1:

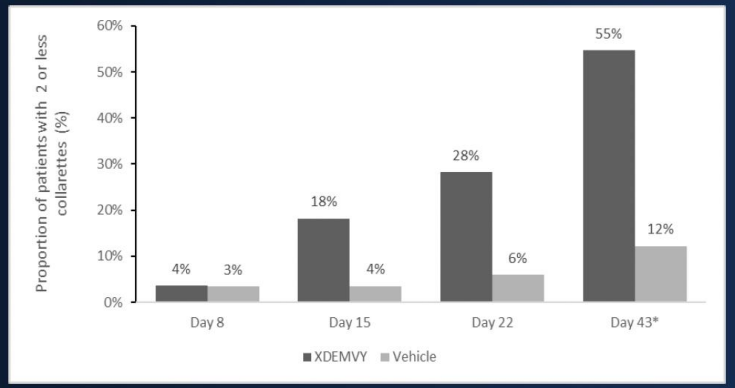
Proportion of patients with 2 or less collarettes for the upper eyelid



*Day 43 Primary Endpoint; XDEMVY N=209, Vehicle N=204, p-value <0.01

Figure 2. Saturn-2:

Proportion of patients with 2 or less collarettes for the upper eyelid



*Day 43 Primary Endpoint; XDEMVY N=193, Vehicle N=200, p-value <0.01

SG

Ocular Adverse Event Summary

- **Overall, there were low rates of ocular AEs across both studies**

Saturn-1: Treatment-Related Ocular AE Rates >1%[1]

	TP-03 (n=212)	Vehicle (n=209)
Instillation Site Pain/Burning/Stinging	25 (11.8%)	16 (7.7%)
Instillation Site Pruritus	3 (1.4%)	7 (3.3%)
Visual Acuity Reduced	3 (1.4%)	5 (2.4%)
Eye Pain	3 (1.4%)	2 (1.0%)
Eye Discharge	3 (1.4%)	1 (0.5%)
Dry Eye	0	1 (0.5%)
AE Severity	All mild	1 moderate All others mild

Saturn-2: Treatment-Related Ocular AE Rates >1%[2]

	TP-03 (n=203)	Vehicle (n=209)
Instillation Site Pain/Burning/Stinging	16 (7.9%)	14 (6.7%)
Instillation Site Pruritus	1 (0.5%)	1 (0.5%)
Visual Acuity Reduced	1 (0.5%)	3 (1.4%)
Eye Pain	1 (0.5%)	0
Eye Discharge	1 (0.5%)	0
Dry Eye	3 (1.5%)	1 (0.5%)
AE Severity	3 moderate All others mild	1 moderate All others mild

All treatment-related ocular AEs were mild or moderate

AE, adverse event.

1. Yeu E et al. Cornea. 2022. Ahead of print. doi:10.1097/ICO.0000000000030972. 2. Karpecki P et al. Abstract presented at: American Academy of Optometry Annual Meeting. October 2022; San Diego, CA.

SG

Key Takeaways of Management Approaches

- Current strategies do not effectively kill the *Demodex* mite[1-3]
- Tea tree oil has shown the potential to negatively impact meibomian gland epithelial tissue in vitro[4,*]
- Lack of efficacy and/or poor tolerability of treatments may lead to poor compliance[2,3]
- Ideal treatment:[1-3]
  - Undergone randomized controlled trials
  - FDA-approved
  - Easy to use
  - Minimal side effects
  - Low toxicity
  - Quick, permanent and long-lasting mite eradication

*Results of an in vitro study on immortalized human meibomian gland epithelial cells.
FDA, US Food and Drug Administration.

1. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 2. Zhang AC et al. *Ophthalmic Physiol Opt.* 2020;40(4):389-432. 3. Lam NSK et al. *Parasitology.* 2020;147(14):1587-1613.

SG

Course Summary

- *Demodex* blepharitis:
  - Is prevalent (present in 60% of Americans visiting eye care providers) and often misdiagnosed, as symptoms overlap with many other ocular conditions
  - Impacts psychosocial functioning and quality of life in patients
- Diagnosis of *Demodex* blepharitis can be confirmed by asking patients to look down during slit lamp examinations
  - Checking for collarettes, the pathognomonic sign, should be a part of routine eye exams for all patients
- There are no current FDA-approved treatments for *Demodex* blepharitis
- Current management strategies lack efficacy and tolerability, and are associated with poor compliance and results
- Clinical trial results of lotilaner ophthalmic solution, 0.25% show promise in the eradication of the *Demodex* mite and associated signs/symptoms of *Demodex* blepharitis

FDA, US Food and Drug Administration.

PK

Thank you

Questions?