

Blepharitis: The Biggest Unmet Need in Eyecare

Ben Gaddie, O.D. FAAO
 Chief Medical Officer
 Keplr Vision
 Gaddie Eye Centers
 Louisville, KY

1

Financial Disclosures

- Consultant: Tarsus, Bausch and Lomb, Ocusoft

2

What Is Blepharitis?

- Traditionally taught it is either anterior or posterior
- Anterior blepharitis was traditionally caused by bacterial overgrowth, staph endotoxin etc
- Posterior blepharitis was eventually referred to as Meibomian Gland Dysfunction
- I think they got it all wrong, TFOS/DEWS agrees with me!

3

What is MGD?

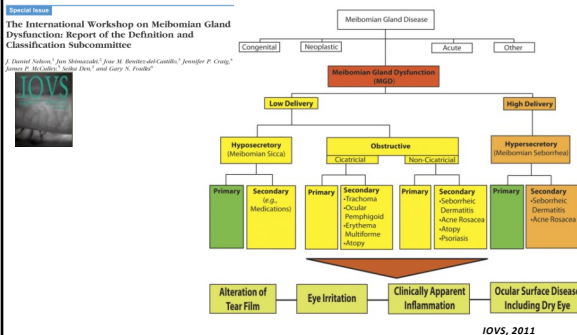
The Workshop defined MGD as follows:

Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.



4

Classifications of MGD



5

TFOS DEWS II - Diagnostic Methodology

James S. Wolffsohn, FCOptom, PhD¹; Correspondence information about the author FCOptom, PhD James S. Wolffsohn Email the author FCOptom, PhD James S. Wolffsohn, Reiko Arita, MD, PhD, Robin Chalmers, OD, Ali Djalilian, MD, Murat Dogru, MD, PhD, Kathy Dumbleton, MCOptom, PhD, Preveya K. Gupta, MD, Paul Karppeck, OD, Shem Lareg, MD, Helio Fult, MSc (Optom), PhD, Benjamin D. Sullivan, PhD, Alan Tomlinson, FCOptom, DSc, Louis Tong, FRCS, PhD, Edoardo Villani, MD, Kyung Chul Yoon, MD, PhD, Lyndon Jones, FCOptom, PhD, Jennifer P. Craig, MCOptom, PhD

1. Introduction
2. Goals of the Diagnostic Methodology Subcommittee
3. Definition of dry eye disease (DED)
4. Classification of sub-categories of dry eye disease (DED)
5. Diagnostic considerations
6. Recommendations of appropriate tests for diagnosis and assessment of dry eye
7. Monitoring dry eye disease progression and management
8. Clinical protocol for dry eye diagnostic test battery
9. Differential diagnosis & comorbidities
10. Emerging technologies
11. Summary and conclusions
12. Financial disclosures
13. Acknowledgements
14. References
15. Tables
16. Questionnaire Forms (DEQ-5 & OSDI)

6

6.8.1.1 Anterior

Anterior eyelid features, such as anterior blepharitis and demodex blepharitis, are differential diagnoses and comorbidities of DED rather than diagnostic criteria and therefore are discussed in Section 9.

6.8.1.2 Posterior

6.8.1.2.1 Lid wiper epitheliopathy (LWE)

A small portion of the marginal conjunctiva of the upper and lower lid acts as a wiping surface to spread the tear film over the ocular surface [379,380]. This contacting surface at the lid margin has been termed the "lid wiper" [379]. The normal lid wiper is rich in goblet cells [381], and appears to be the most sensitive conjunctival tissue of the ocular surface [382]. Lid wiper staining with dyes such as fluorescein and lissamine green, which occurs principally in DED patients [298,299,379,383,384], has been termed lid

7

9.2 Anterior blepharitis

Inflammation of the eyelids can result from infection by, or allergic reaction to, external agents. The clinical features of blepharitis include redness, exanthema, sores, eschar, swelling, and bullous formation. Blepharitis is classified according to its anatomic location. Anterior blepharitis affects the base of the eyelashes, eyelash follicles, and/or eyelid skin. Inflammation of follicles is categorized as marginal blepharitis, whereas that of eyelid skin is blepharo-dermatitis. The pathogenesis of anterior blepharitis is infectious or noninfectious in nature, and so the location and cause of the condition should be considered for diagnosis [523]. Clinical features of anterior blepharitis often overlap those of DED [524]. Recurrent or persistent blepharitis can cause DED, thus observation of the eyelid is important for adequate diagnosis of DED. The tear meniscus, tear film breakup time and pattern, foamy discharge and debris in the tear film should be observed [524], along with the eyelid position (i.e., ectropion and entropion), eyelid closure (i.e., lagophthalmos), blink response and the anterior eyelid margin (noting any collarettes around eyelashes). Staphylococcal or seborrheic anterior blepharitis are linked to ADDE [482,524] in 50–75% of cases [525,526], perhaps due to the decreased tear volume supporting less lysozyme or immunoglobulins [526]. Definitive diagnosis is made by identification of the responsible microorganism or allergen. There are no specific clinical diagnostic tests for blepharitis. However, cultures of the eyelid margins may be indicated for patients who have recurrent anterior blepharitis with severe inflammation as well as for patients who are not responding to therapy [524].

8

9.3 Demodex

Demodex mites are common elongated microscopic ectoparasites that live on the surface of the human body. Demodex infestation is related to age with 84% of the population at age 60 and 100% of those older than 70 years exhibiting Demodex infestation [527]. Demodex can spread from the face to the eyelids, perhaps leading to blepharitis and also rosacea [527–530], which may be the link between DED and meibomian gland dysfunction [528,531–533]. However Demodex infestation can also be found in asymptomatic patients [529]. Contact lens wearers do not show higher rates of Demodex infestation than non-wearers, but the relationship with DED symptoms and signs has not been investigated [534]. Two species, Demodex folliculorum and Demodex brevis have been identified in human eyelids [529,535,536]. Demodex folliculorum are typically found in the lash follicles of the eyelids, whereas Demodex brevis burrow deep into sebaceous and meibomian glands. Sebum is thought to be their main food source and Demodex mites may consume follicular and glandular epithelial cells, which may lead to direct damage of the lid margin [529]. Demodex mites can cause blepharitis by carrying bacteria on their surface including streptococci and staphylococci [529,537]. Also the protein inside the Demodex mites and their waste products may trigger inflammatory responses, likely via a delayed hypersensitivity or an innate immune response [538]. Demodex-based lid margin inflammation may result in blepharoconjunctivitis [529]. Proper treatment of ocular demodicosis may resolve blepharoconjunctivitis in adults [529,539], however its role in children remains unclear [529]. Severe cases of demodex with inflamed lid margins can affect the cornea [529,540].

Demodex can sometimes be observed in situ with high magnification slit lamp microscopy, on epilated lashes using standard light microscopy or using more advanced techniques, such as IVCM [329,440,528,529,541]. Liu et al. [529] recommend the following clinical procedure based on a comprehensive literature review:

1. Clinical history: high index of suspicion when blepharitis, conjunctivitis or keratitis in adult patients or blepharoconjunctivitis or recurrent chalazia in young patients are refractory to conventional treatments, or when there is madarosis or recurrent trichiasis.
2. Slit-lamp examination: typical cylindrical dandruff at the root of eyelashes.
3. Microscopic confirmation: detection and counting of Demodex eggs, larvae and adult mites on epilated lashes.


To avoid epilating eyelashes it has also been reported that Demodex leave the follicle and are visible by slit lamp microscopy after gentle tension is applied to the lash and the lash manually rotated with forceps, encouraging exodus of the mites and allowing the lash to "scrape out" Demodex deep within the follicle [542]. As Demodex infestation can also occur in non-DED patients [527], its diagnostic contribution is limited.

9

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 understood¹
- Factors such as immunosuppression, diabetes, and sebaceous hyperplasia may contribute to increased Demodex proliferation—a contributor of inflammatory responses associated with rosacea¹
- 59% of patients presenting with facial rosacea have Demodex infestation^{2,*}



*This research involved analysis of 40 patients, whose 40% may contribute toward to identify antibodies and specific immune biomarkers.
1. Demodex. Journal of the American Academy of Dermatology. 2019;81(2):201-208. doi:10.1016/j.jaad.2018.09.046. Epub 2019 Feb 14. PMID: 30300000

BC

10

An Bras Dermatol. 2020;95(2):187-193

Anais Brasileiros de Dermatologia

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Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis^{1,2,*}

Ezgi Aktaş Karabay ¹, Aslı Aksu Çerman ²

Department of Dermatology and Venereology, Faculty of Medicine, Başçeşir University, Istanbul, Turkey

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Available online 12 February 2020

11

INVESTIGATION

Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis^{1,2,*}

Ezgi Aktaş Karabay ¹, Aslı Aksu Çerman ²

Department of Dermatology and Venereology, Faculty of Medicine, Başçeşir University, Istanbul, Turkey

Received 18 March 2019; accepted 26 August 2019
Available online 12 February 2020

KEYWORDS
Acne vulgaris; Demodex; seborrheic dermatitis; Rosacea

Abstract
Background: Demodex mites are found on the skin of many healthy individuals. Demodex mites in high densities are considered to play a pathogenic role.
Objective: To investigate the association between Demodex infestation and the three most common facial dermatoses: acne vulgaris, rosacea and seborrheic dermatitis.
Methods: This prospective, observational case-control study included 127 patients (43 with acne vulgaris, 47 with rosacea and 37 with seborrheic dermatitis) and 77 healthy controls. The presence of demodexes was evaluated by standardized skin surface biopsy in both the patient and control groups.
Results: In terms of gender and age, no significant difference was found between the patients and controls (p > 0.05). Demodex infestation rates were significantly higher in patients than in controls (p < 0.001). Demodex infestation rates were significantly higher in the rosacea group than acne vulgaris and seborrheic dermatitis groups and controls (p < 0.001, p < 0.024, p < 0.001, respectively). Demodex infestation was found to be significantly higher in the acne vulgaris and seborrheic dermatitis groups than in controls (p < 0.001 and p < 0.001, respectively). No difference was observed between the acne vulgaris and seborrheic dermatitis groups in terms of demodexes (p = 0.294).
Study limitations: Small sample size is a limitation of the study. The lack of an objective scoring system in the diagnosis of Demodex infestation is another limitation.

12

> Clin Exp Dermatol. 2009 Dec;34(8):e516-20. doi: 10.1111/j.1365-2230.2009.03343.x. Epub 2009 May 22.

Is Demodex folliculorum an aetiological factor in seborrhoeic dermatitis?

Y Karıncaoğlu ¹, B Tepe, B Kalaycı, M Atambay, M Seyhan

Affiliations + expand
PMID: 19486039 DOI: 10.1111/j.1365-2230.2009.03343.x

Abstract

Background: Seborrhoeic dermatitis (SD) is a common inflammatory skin disease for which no single cause has been found, although many factors have been implicated. The mite Demodex folliculorum (DF) is most commonly seen in the pilosebaceous unit in humans. SD is located in areas that are rich in sebaceous glands, which are also preferred by DF.

Aims: To compare the number of DF parasites in patients with clinical SD and in healthy controls, and to investigate any possible relationship between the number of DF mites and the presence of SD.

Methods: The study comprised 38 patients with SD and 38 healthy controls. Standard random and lesion-specific sampling was performed in the group of patients with SD, whereas standard random sampling only was performed for controls.

Results: Demodex folliculorum sampling was positive in 19 patients (50%) and 5 controls (13.1%). Mean DF density was 8.16 +/- 10.1/cm(2) (range 0-40) and 1.03 +/- 2.17/cm(2) (1-7) in patient and control groups, respectively. The differences between groups for DF positivity and mean DF density were significant (P = 0.001 for each). DF was found in 13 lesional areas in the patient group, but in only 5 areas in the control group (P = 0.031).

Conclusions: The number of DF mites was significantly higher in both lesional and nonlesional areas of patients with SD. This suggests that, when other aetiological causes are excluded, DF

13

Allergy

Demodex mites
Link to allergic conjunctivitis
Increase secretion cytokine (IL-17)
Stimulates inflammatory or allergic reactions
Resulting ocular surface damage.

Koo H, Kim TH, Kim KW, et al. Ocular surface discomfort and demodex: effect of tea tree oil eyelid scrub in demodex blepharitis. J Korean Med Sci. 2012 Dec;27(12):1574-9.

Kim JT, Lee SH, Chun YS, Kim JC. Tear cytokines and chemokines in patients with Demodex blepharitis. Cytokine. 2011;53:94-99.

14

Rosacea


Rosacea and demodex
Meta-analysis of 48 studies
10 different countries
28,527 subjects
Rosacea patients 7-8x chance have Demodex

Zhao YE, Wu LP, Peng Y, Cheng H. Retrospective analysis of the association between Demodex infestation and rosacea. Arch Dermatol 2010;146:896Y902.


15

Demodex Has Been Linked to Rosacea and Blepharitis

Slide courtesy of Scheffer Tseng, MD
The Ocular Surface Center, Miami Florida



Skin Rosacea





Ocular Rosacea, Blepharitis

Coston, 1967, English, 1971, English & Nutting, 1981, Heacock, 1986, Fulk & Clifford, 1990, Fulk et al, 1996, Kamoun et al. 1999, Morfin, 2003

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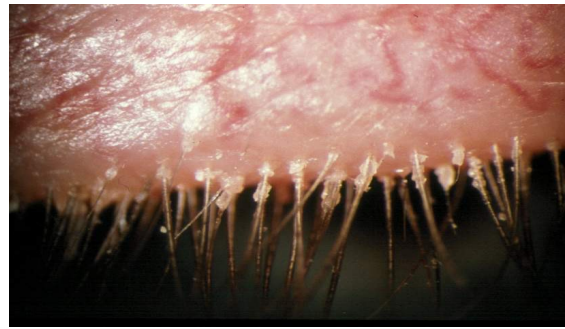
Demodex Infestation is Associated with Floppy Eyelid Syndrome ⁽⁴⁾

- floppy, rubbery and easily everted upper eyelids
- lacrimal gland prolapse
- ptosis/lash ptosis
- dematochalasis
- eye lid hyperpigmentation.
- papillary conjunctivitis.
- squamous metaplasia and keratinization in meibomian glands/gland dysfunction
- lax lids have diminished lipid production
- associated with obstructive sleep apnea

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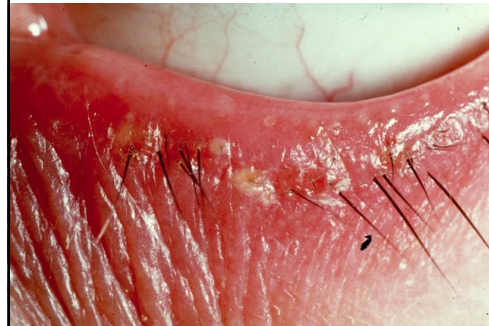
Anterior Blepharitis



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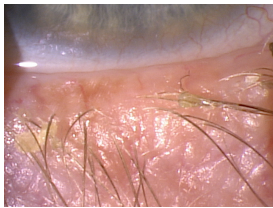


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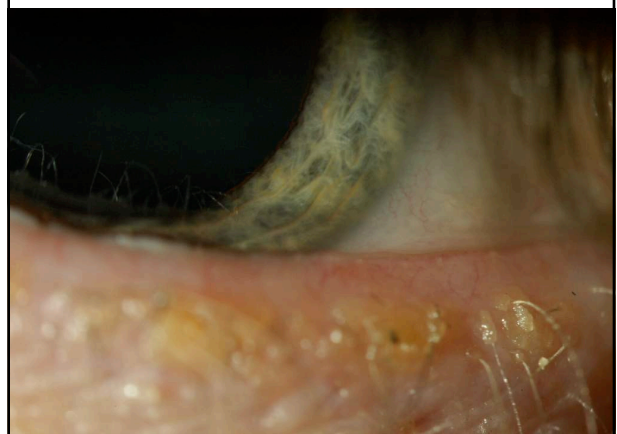


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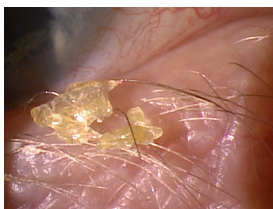
Seborrheic Blepharitis



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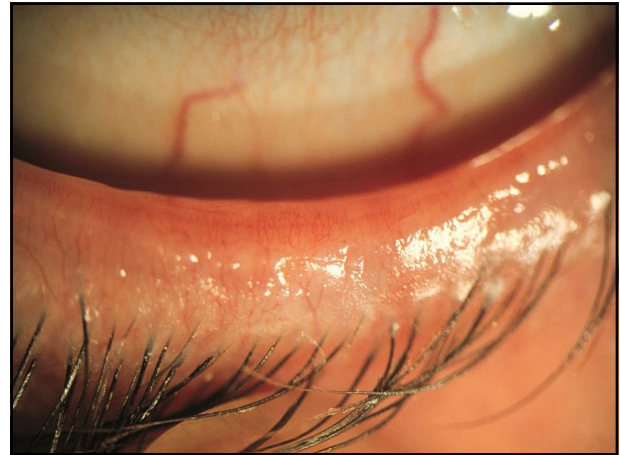
Rosacea

- Erythema
- Telangiectasia
- Pustules
- Prominent sebaceous glands
- Rhinophyma

24



25



26

What Do We Know?

- Blepharitis and MGD are extremely common
- Demodex is extremely common
- Lid disease is a common cause of evaporative dry eye
- Rosacea is a common cause of MGD
- Demodex is a common cause of Rosacea
- What we thought was anterior blepharitis is probably Demodex
- Ocular allergy symptoms overlap dry eye and MGD symptoms

27

What We Really DON'T Know:

- What is the true prevalence of Demodex?
- How much Demodex results in symptoms
- How much "symptom" is needed to treat
- Which percentage of dry eye is really lipid layer evaporation vs. mucin deficiency
- What is an effective and enduring treatment for MGD?
- What is an effective and enduring treatment for Demodex?

28

What We Really DON'T Know:

- Could there be a socioeconomic predisposition to demodex?
- Are autoimmune systemic conditions associated with blepharitis?
- Are there differences in prevalence rates by ethnicity or gender?

29



HANDBOOK OF MEDICAL ENTOMOLOGY

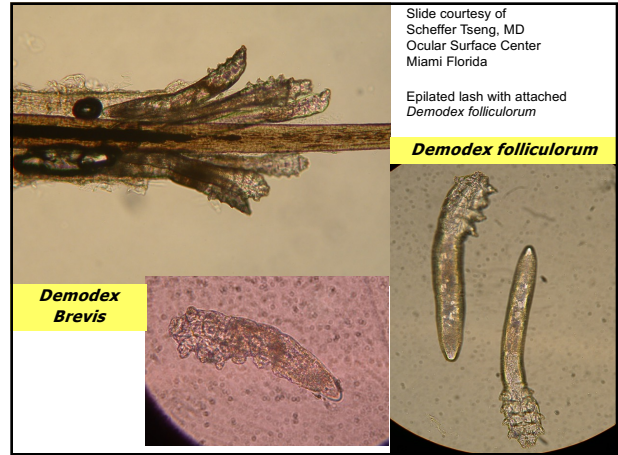
Dr. WM. A. RILEY, Professor of Insect Morphology and Parasitology, Cornell University
 Dr. O. A. JOHANNSEN, Professor of Biology, Cornell University

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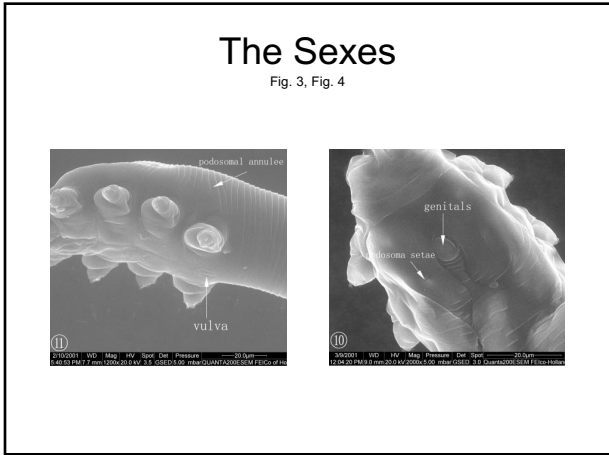
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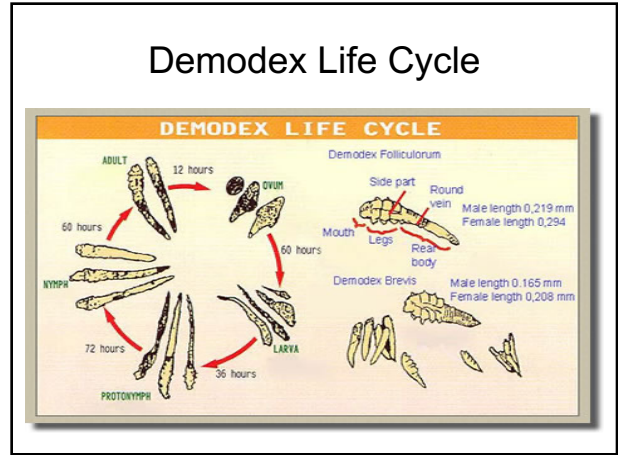
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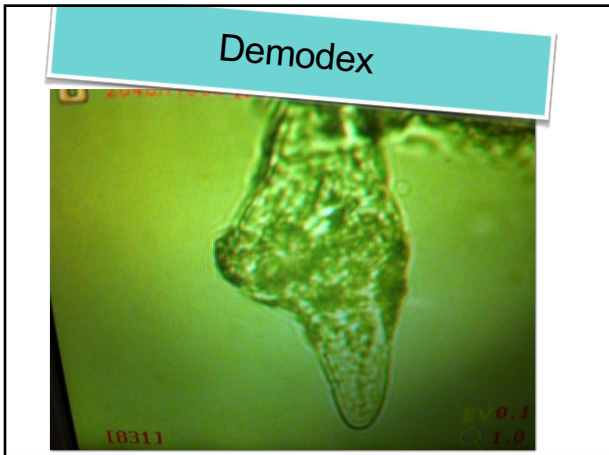
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Clinical history

Symptoms:
Itch, burning, foreign body sensation,
crusting, redness, blurry vision

[Hom MM](#), [Mastrota KM](#), [Schachter SE](#). Demodex. Optom Vis Sci. 2013 Jul;90(7):e198-205.

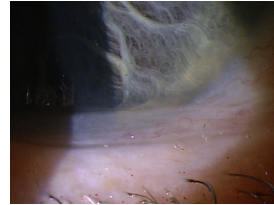
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Symptoms of Demodex

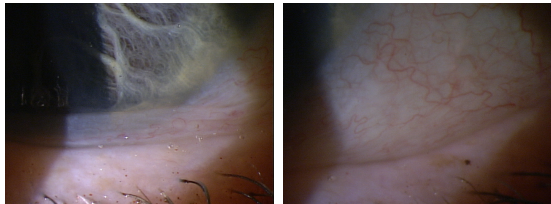
- Eyelid itching
- Ocular itching
- Facial itching
- Thickened, red lids seen
 - Personal observation: Exacerbated in PGA pts
- **Watering, often chronic**
- Eyelash loss
- Chronic redness of conjunctiva
- Coexists with OSD and MGD symptoms

37

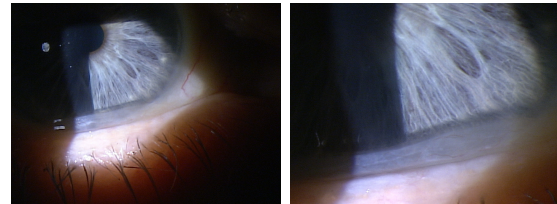
Redundant Conjunctival Folds



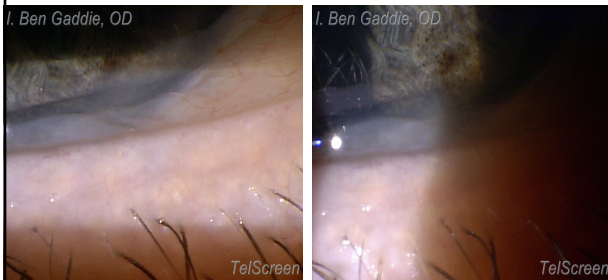
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41

2. Slit lamp evaluation

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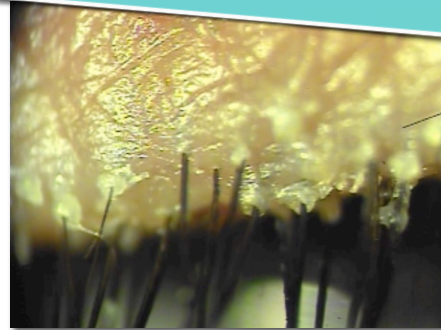
Cylindrical dandruff

“Cylindrical dandruff was pathognomonic for the presence of demodex infestation.”

Gao YY, Di Pascuale MA, Li W, et al. High Prevalence of Demodex in Eyelashes with Cylindrical Dandruff. Invest. Ophthalmol. Vis. Sci. 2005;46(9):3089-3094.

43

Cylindrical dandruff



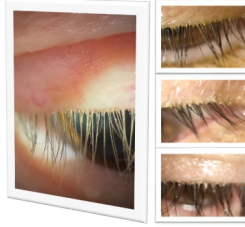
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Collarettes Are the Pathognomonic Sign of Demodex Blepharitis

Confirming the presence of collarettes can be used to confidently make a diagnosis

- In a clinical study, *Demodex* mites, detected via epilation, were found on 100% of lashes with collarettes²
- In another clinical study, *Demodex* mites, detected via molecular technique (PCR), were found on 100% of lashes with collarettes²

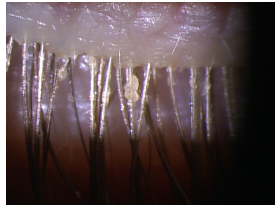
- Collarettes are composed of mite waste and eggs
- Regurgitated undigested material combined with epithelial cells, keratin, mite eggs, and digestive enzymes, which cause irritation^{1,4}
 - Translucent, waxy plugs typically at base of lashes³



Photos courtesy of Elizabeth Yu, MD, Paul Singh, MD, Paul Karpavicius, MD, and Jeff Goldstein

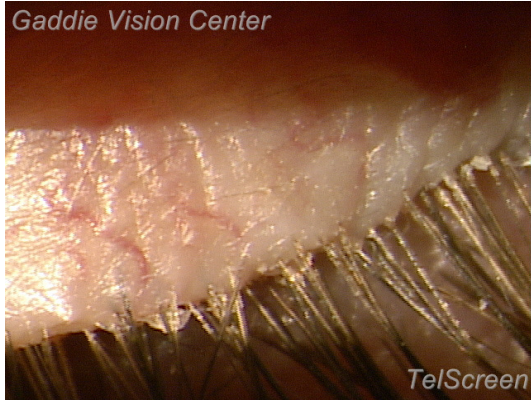
45

1. Gao YY, Di Pascuale MA, et al. High prevalence of demodex in eyelashes with cylindrical dandruff. Invest Ophthalmol Vis Sci. 2005;46(9):3089-3094. 2. Gao YY, Di Pascuale MA, et al. High prevalence of demodex in eyelashes with cylindrical dandruff. Invest Ophthalmol Vis Sci. 2005;46(9):3089-3094. 3. Gao YY, Di Pascuale MA, et al. High prevalence of demodex in eyelashes with cylindrical dandruff. Invest Ophthalmol Vis Sci. 2005;46(9):3089-3094. 4. Gao YY, Di Pascuale MA, et al. High prevalence of demodex in eyelashes with cylindrical dandruff. Invest Ophthalmol Vis Sci. 2005;46(9):3089-3094.



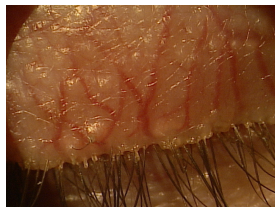
46

Gaddie Vision Center



TelScreen

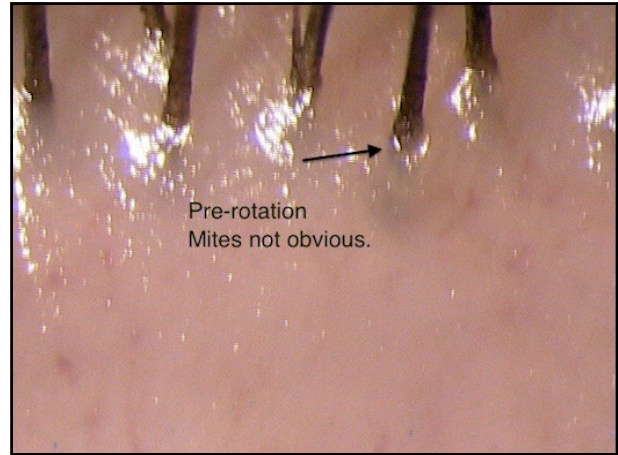
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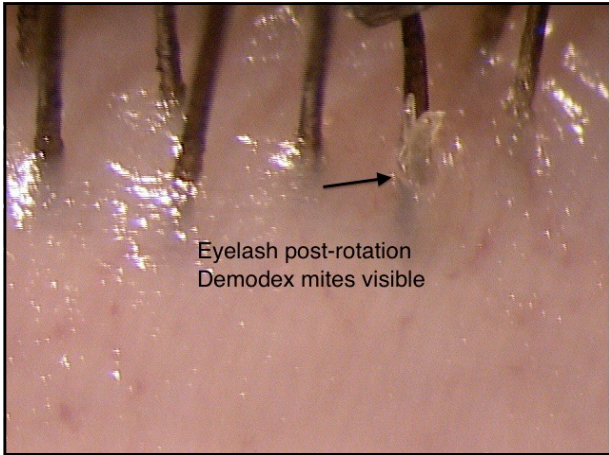
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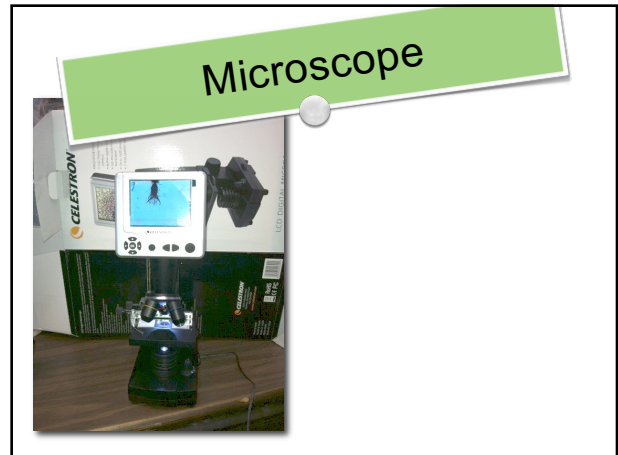
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52

3. Epilate and microscope

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54

Demodex

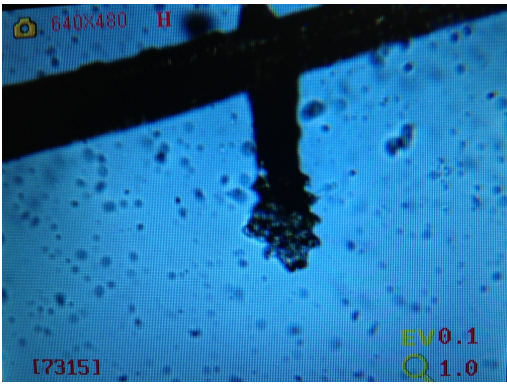
Tip sheet
Drop cover slip first, then add emulsion drop at the side
Show and tell

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Demodex



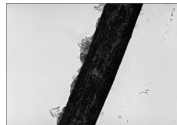
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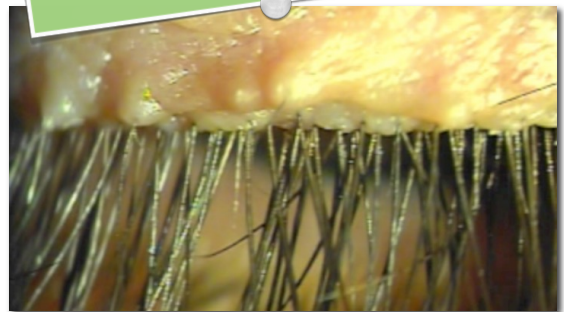


58



59

Distention



60



61



62

The ROYAL COLLEGE of OPHTHALMOLOGISTS

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ARTICLE OPEN

Clinical diagnosis and management of *Demodex* blepharitis: the *Demodex* Expert Panel on Treatment and Eyelid Health (DEPTH)

Brandon D. Ayres¹, Eric Donnemfeld², Majan Farid³, Ian Benjamin Gaddie⁴, Preya K. Gupta^{1,5}, Edward Hellanz⁶, Paul M. Karpecki⁷, Richard Lindstrom⁸, Kelly K. Nichols^{9,10}, Stephen C. Pflugfelder¹¹, Christopher E. Star¹² and Elizabeth Yu^{1,13}

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BACKGROUND: Twelve ocular surface disease experts convened to achieve consensus about *Demodex* blepharitis (DB) using a modified Delphi panel process.

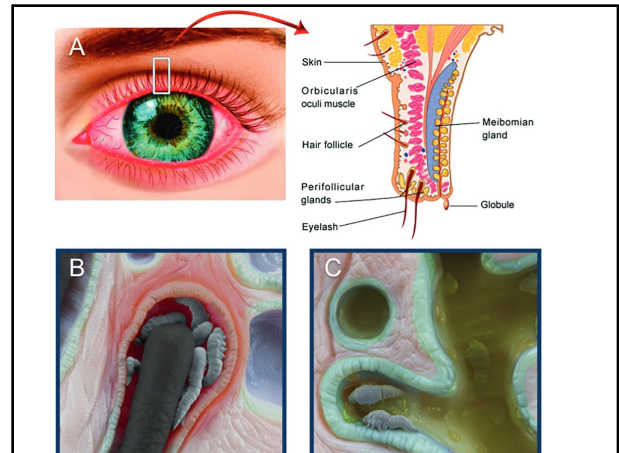
METHODS: Online surveys were administered using scaled, open-ended, true/false, and multiple-choice questions. Consensus for questions using a 1 to 9 Likert scale was predefined as median scores of 7–9 and 1–3. For other question types, consensus was achieved when 8 of 12 panelists agreed. Questions were randomized, and results of each survey informed the following survey.

RESULTS: Twelve practitioners comprised the *Demodex* Expert Panel on Treatment and Eyelid Health (DEPTH). Following 3 surveys, experts agreed that DB is chronic ($n = 11$) and recurrent ($n = 12$) and is often misdiagnosed. Consensus was achieved regarding inflammation driving symptoms (median = 7; range 7–9), collarettes as the most common sign ($n = 10$) and pathognomonic for DB (median = 9; range 8–9), and itching as the most common symptom ($n = 12$). Panelists agreed that DB may be diagnosed based on collarettes, mites, and/or patient symptoms ($n = 10$) and felt that patients unresponsive to typical therapies should be evaluated for DB ($n = 12$). Consensus about the most effective currently available OTC treatment was not reached.

CONCLUSIONS: The Delphi methodology proved effective in establishing consensus about DB, including signs, symptoms, and diagnosis. Consensus was not reached about the best treatment or how to grade severity. With increased awareness, eyecare practitioners can offer DB patients better clinical outcomes. A follow-up Delphi panel is planned to obtain further consensus surrounding DB treatment.

Eye: <https://doi.org/10.1038/s41433-023-02500-4>

63



64

Table 1. Key areas of consensus on scaled questions.

Area of consensus	Median score	Range
Collarettes are pathognomonic for <i>Demodex</i> blepharitis	9	8–9
Epilation is not necessary	9	5–9
Number of mites correlates with density and severity of collarettes	9	4–9
<i>Demodex</i> blepharitis may cause insecurity about appearance	8	6–9
Number of mites correlates with symptom severity	8	6–9
Restoring balance to the ocular ecology is the key to managing <i>Demodex</i> infestation	8	5–9
More itching is seen in dry eye disease with <i>Demodex</i> blepharitis vs. <i>Demodex</i> blepharitis alone	8	5–9
<i>Demodex</i> blepharitis patients may have secondary ocular infections	7.5	2–9
Contact lens intolerance correlates with <i>Demodex</i> infestation	7	7–9
<i>Demodex</i> mites and their byproducts such as chitin and digestive enzymes trigger the inflammatory cascade	7	7–9
Inflammation drives symptoms in <i>Demodex</i> blepharitis	7	7–9
Itching is caused by non-histamine pathways	7	4–9
Lash loss only occurs with severe <i>Demodex</i> blepharitis	7	1–9
Mite visualization NOT necessary to diagnose	2	1–8

65

Blepharitis Is a Large and Underserved Market in Eye Care

Epidemiology of *Demodex* Blepharitis

- Estimated In-Office Epidemiology: ~25M
- Population Epidemiology: ~5M
- Current ICD-10: ~1M Dx/yr
- ~45% with blepharitis¹⁴
- ~45% with *Demodex* infestation¹⁵
- ~43M unique adult ECP visits¹⁶
- ~10% with collarettes¹⁷
- ~2.1M blepharitis ICD-10-CM Dx visits¹⁸
- ~1.5Myr Disease¹⁹
- Disappears no mite education²⁰

Approx. 9-25M U.S. *Demodex* Blepharitis Prevalence

Large Patient Population with Significant Disease Impact

- Significant Head Start on Diagnosis
- Blepharitis Reactivity Causes
- Blepharitis Can Lead to
- Concomitant Dry Eye
- Blepharitis and Surgery
- Contact Lens Drop-out
- Prescription Treatment

75% (collarettes clinic prevalence) and 66% (disease impact studies demonstrate high prevalence of disease and significant burden on patients)

- 2.3M ICD-10 Blepharitis Dx visits¹⁸
- Itching of eyes, redness, irritation and itchy, with debris on the eyelashes²¹
- Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea²²
- Significant overlap in Dry Eye patients. *Demodex* prevalent in 15% of DE patients²³
- Important factor for maintaining surgical outcomes²⁴
- 57% of Cataract Patients have *Demodex* blepharitis²⁵
- Studies have shown a direct correlation between *Demodex* blepharitis and Contact Lens intolerance²⁶
- None, 62% of patients currently seeking treatment²⁷

66

Prevalence of Demodex Blepharitis

Up to 25 million individuals in the United States suffer from Demodex blepharitis.^{1-4, 7, 12}

~80% of patients visiting eye clinics each year have collarettes^{1,4,5}

- 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 blepharitis⁵⁻⁸

- 89% of patients with blepharitis
- 80% 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.
 †Data is for an analysis of 100 eyelashes collected from 100 patients with Demodex blepharitis.
 ‡Per a retrospective analysis of patients at 8 eye clinics who underwent slit lamp examinations.
 §As confirmed by the presence of collarettes.

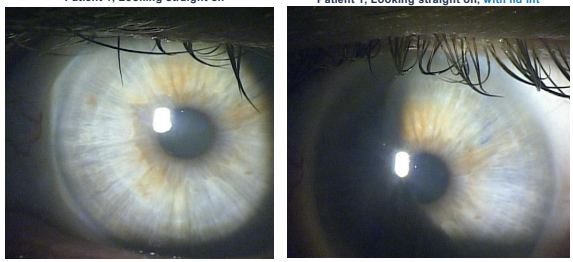
DG

67

Collarettes Can Be Easily Missed on the Upper Lid!

Patient 1, Looking straight on

Patient 1, Looking straight on, with lid lift

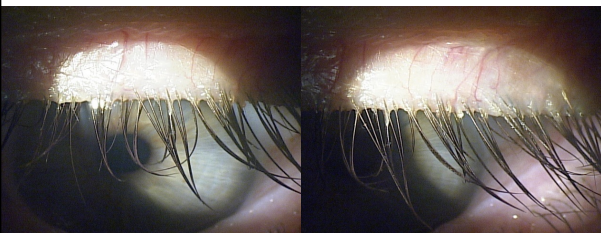


c/o E. Yeu, MD, 1.0 mag

68

Collarettes Can Be Easily Seen on the Upper Lid when Patient Looks DOWN

Patient : Diffuse collarettes, misdirected and missing lashes



c/o E. Yeu, MD, 1.0 mag

69

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

PK

70

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

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71

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

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72

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**

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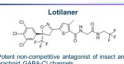
73

TP-03 is a Novel Therapeutic Designed to Eradicate Demodex Mites and Treat Demodex Blepharitis

Product Form	Multi-dose eye drop solution bottle, preserved
Targeted Use	Treatment of Demodex blepharitis
MOA	Paralysis and death of Demodex mites
Diagnosis	Collarettes identified in standard eye examination
Dosing	BID* for 6 weeks
Efficacy Goal	1 st collarette cure, 2 nd mite eradication, 2 nd redness + collarette cure
Safety Goal	Well-tolerated safety profile



Lotilaner



- Potent, non-competitive antagonist of insect and arachnid GABA_A receptors
- Highly lipophilic molecule

*twice daily per day

74

Extensive Clinical Trial Program for TP-03

Study	# of Subjects	Effectiveness Endpoints	Study Highlights	Status
PoC: Mercury	80 mites	Ex-vivo mite death count	Ex-vivo mite testing	Completed
P2a: Mars	15 - Single arm	Collarette grade Mite density	28-day BID dosing	Completed
P2b: Jupiter	60 - 1:1	1 st - Collarette grade 2 nd - Mite density	28-day BID dosing; RCT	Completed
P2a: Io	18	1 st - Collarette cure 2 nd - Mite eradication	Crossover of Jupiter control arm subjects; 42-day BID dosing	Completed
P2b: Europa	54 - 1:1	1 st - Collarette cure 2 nd - Mite eradication 2 nd - Redness composite	42-day BID dosing; RCT	Completed
P2b/3: Saturn-1	421 - 1:1	1 st - Collarette cure 2 nd - Mite eradication 2 nd - Redness composite	Pivotal registration study 42-day BID dosing; RCT	Completed
P3: Saturn-2	418 - 1:1	1 st - Collarette cure 2 nd - Mite eradication 2 nd - Redness composite	Pivotal registration study 42-day BID dosing; RCT	Initiated May 2021

Two Pivotal Trials

1st - Same formulation of TP-03 as expected in the Saturn trials
2nd - Reference product trial

75

ARTICLE IN PRESS

AMERICAN ACADEMY OF OPHTHALMOLOGY

Lotilaner Ophthalmic Solution 0.25% for Demodex Blepharitis

Randomized, Vehicle-Controlled, Multicenter, Phase 3 Trial (Saturn-2)

Ian Benjamin Gaskie, OD,¹ Eric D. Donnenfeld, MD,² Paul Karpecki, OD,³ Patrick Valtner, OD,⁴ Gregg J. Beedy, MD,⁵ Jared D. Peterson, MD,⁶ Blake Simmons, OD,⁷ Anne R.P. Edell, MD,⁸ William E. Whitson, MD,⁹ Joseph B. Calvo, MD,¹⁰ Stephanie N. Bates, OD,¹¹ Mark Holdbrook, BA,¹² Joel Treviño, MD, PhD,¹³ John Meyer, MD,¹⁴ Elizabeth Yee, MD,¹⁵ Saturn-2 Study Group

76

Saturn-1 Patient Enrollment and Follow-up

6 Week Treatment and Follow-up, twice a day drop without any touching or wiping of lid margin

```

    graph TD
      R[Randomized n=421 at 15 sites in USA] --> TP03[TP-03 n=212]
      R --> V[Vehicle n=209]
      TP03 --> D1[Discontinued n=3]
      TP03 --> C1[Completed 6 Weeks Treatment n=209]
      V --> D2[Discontinued n=5]
      V --> C2[Completed 6 Weeks Treatment n=204]
      D1 --- COV1[n=3 related to COVID]
      D2 --- AE1[n=1 related AE mild]
      D2 --- AE2[n=1 unrelated AE]
      D2 --- COV2[n=2 related to COVID]
      D2 --- AE3[n=1 other]
    
```

77

Saturn-1: All Primary and Secondary Endpoints Were Met and TP-03 was Well Tolerated

- **Efficacy:** All pre-specified primary, secondary, and exploratory endpoints were met
 - Primary Endpoint: Complete Collarette Cure **p < 0.0001**
 - Clinically Meaningful Collarette Cure (Grade 0 or 1) **p < 0.0001**
 - Secondary Endpoint: Mite Eradication **p < 0.0001**
 - Secondary Endpoint: Composite Lid Erythema and Collarette Complete Cure **p < 0.0001**
 - Clinically Meaningful Composite Lid Erythema and Collarette Complete Cure **p < 0.0001**
 - Secondary Endpoint: Erythema Cure **p = 0.0001** and Erythema Response **p = 0.0002**
 - Rapid Cures: Improvements Seen in 2 Weeks **p ≤ 0.0149** in Primary and Secondary Endpoints
- **Safety:** TP-03 was well-tolerated, with safety profile similar to vehicle
 - All TP-03-related AE's were mild with no treatment related discontinuations
 - 92% of patients reported the drop to be neutral to very comfortable

78

Collarette Grading Scale Used in Saturn-1

- Grade 4: >25 of lashes on lid with collarettes
- Grade 3: Between 10-25 of lashes on lid with collarettes
- Grade 2: Between 5 collarettes to 10 of lashes on lid with collarettes
- Grade 1: 3-10 collarettes on the lashes
- Grade 0: 0-2 collarettes on the lashes

Average baseline

Non-linear scale for counting collarettes performed by each site investigator

79

Lid Margin Erythema Scale Used in Saturn-1

Average baseline 1.5

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

Established and validated scale used in blepharitis studies, performed by each investigator

80

Saturn-1 Baseline Characteristics

	TP-03	Vehicle
Age	66.1	67.8
Female %	58	56
Collarette Score	2.8	2.8
Mite Density	3.2	3.2
Erythema Score	1.5	1.5

81

Clinically Meaningful Collarette Cure

Time Point	TP-03 (%)	Vehicle (%)
Day 8	23%	11%
Day 15	41%	16%
Day 22	60%	18%
Day 43	81%	23%

82

Primary Endpoint of Complete Collarette Cure Achieved

Regulatory Endpoint of Complete Collarette Cure Observed by Week 2

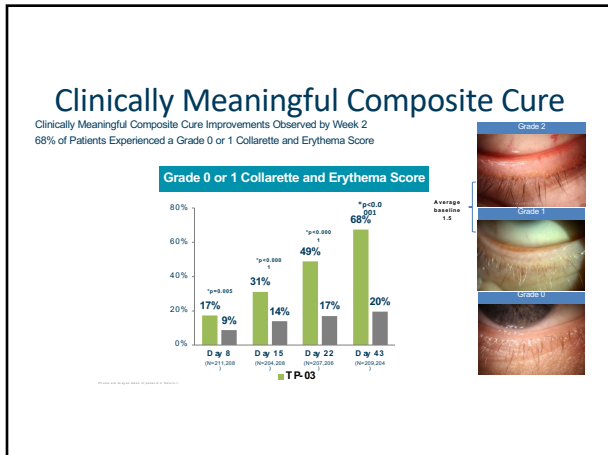
Time Point	TP-03 (%)	Vehicle (%)
Day 8	2%	2%
Day 15	10%	1%
Day 22	18%	2%
Day 43	43%	7%

83

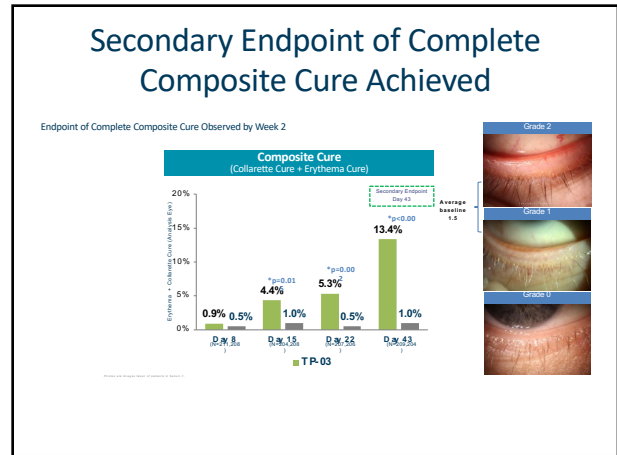
Secondary Endpoint of Mite Eradication Rate Achieved

Time Point	TP-03 (%)	Vehicle (%)
Day 15	33%	9%
Day 22	40%	12%
Day 43	68%	18%

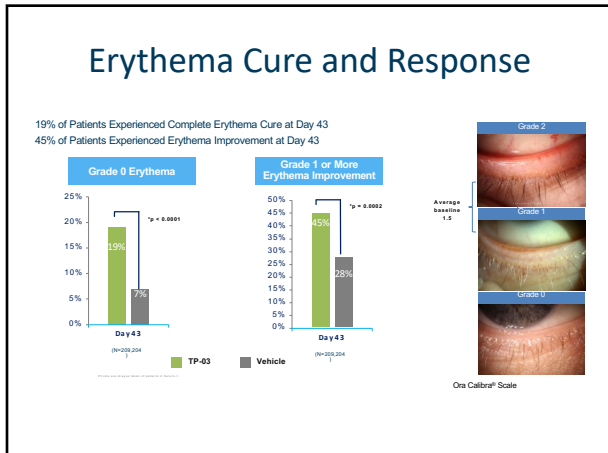
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85



86



87

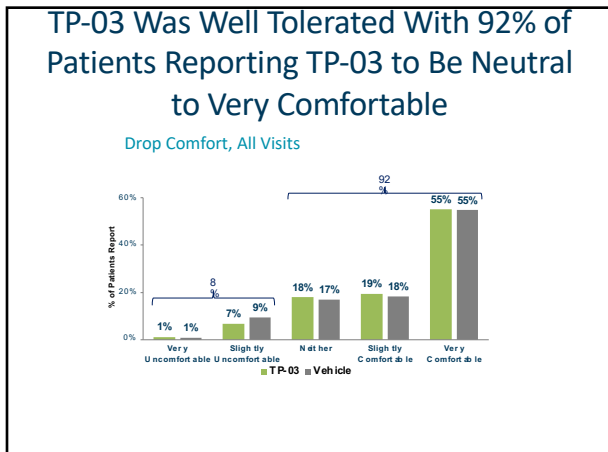
Adverse Event Summary

Treatment related ocular AEs occurring at rate of 2.1% in active group

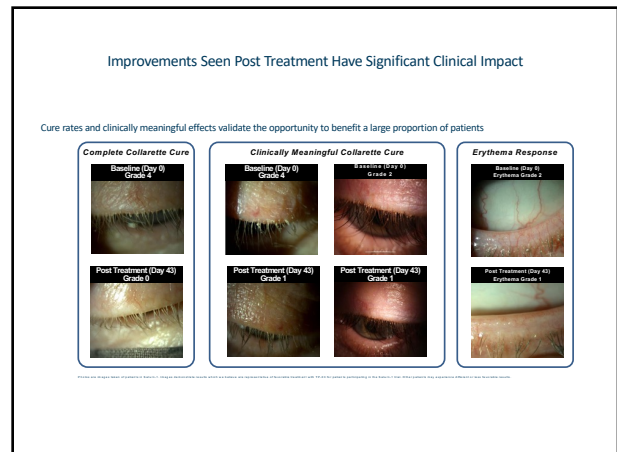
- Summary of Adverse Events occurring at any time during trial

	TP-03 (n=212)	Vehicle (n=209)
Instillation site pain/burning/stinging	25 (11.8%)	16 (7.7%)
Instillation site pruritis	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%)
AE Severity	All Mild	One moderate AE All other AEs mild

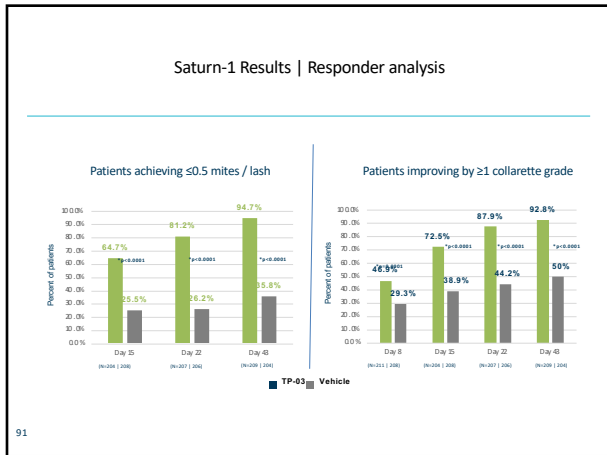
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89



90



91

Two Successful Pivotal Trials with Consistency Across Endpoints

Consistency and High Statistical Significance Expected to Result in Definitive Standard of Care Therapy for Demodex Blepharitis

	Saturn-1 (Pivotal Phase 2b/3) N=421	Saturn-2 (Pivotal Phase 3) N=412	Combined Pivotal Data N=833
Primary Endpoint: Complete Collarette Cure	44% vs. 7% (p<0.0001)	56% vs. 13% (p<0.0001)	50% vs. 10%
Clinically Meaningful Collarette Cure (Grade 0 or 1)	81% vs. 23% (p<0.0001)	89% vs. 33% (p<0.0001)	85% vs. 28%
Mite Eradication	68% vs. 18% (p<0.0001)	52% vs. 14% (p<0.0001)	60% vs. 16%
Lid Erythema Cure	19% vs. 7% (p<0.0001)	31% vs. 9% (p<0.0001)	25% vs. 8%
Safety	Generally safe and well tolerated	Generally safe and well tolerated	Generally safe and well tolerated

92

- ### Current/Previous Treatment methods for Demodex
- Topical Ivermectin
 - Topical Tea Tree Oil
 - Ocusoft Demodex kit
 - Cliradex premedicated towelettes
 - Blephadex towelettes or foam
 - Terpinol-4 Active ingredient in TTO
 - Other homemade concoctions?
 - Macadamia Nut oil

95

REVIEW ARTICLE

Demodex Blepharitis: A Comprehensive Review of the Disease, Current Management, and Emerging Therapies

Michelle K. Rhee, M.D., Elizabeth Yeu, M.D., Melissa Barnett, O.D., FAO, FRCO, Christopher J. Rapuano, M.D., Deepinder K. Dhallwani, M.D., Kelly K. Nichols, O.D., M.P.H., Ph.D., Paul Karypecki, O.D., Francis S. Mah, M.D., Arthur Chan, Ph.D., James Mun, Ph.D., and Ian Benjamin Gaddie, O.D.

Abstract: Demodex blepharitis is a common disease of the eyelid, affecting approximately 25 million Americans. This article reviews what is known about the mechanisms and impact of Demodex blepharitis, risk factors, signs and symptoms, diagnostic techniques, current management options, and emerging treatments. Demodex mites contribute to blepharitis in several ways: direct mechanical damage, as a vector for bacteria, and by inducing hypersensitivity and inflammation. Risk factors for Demodex blepharitis include increasing age, rosacea, and diabetes. The costs, symptom burden, and psychosocial effects of Demodex blepharitis are considerable. The presence of collarettes is pathognomonic for Demodex blepharitis. Rubness, dryness, discomfort, foreign body sensation, lash anomalies, and itching are also hallmarks of the disease. Although a number of oral, topical, eyelid hygiene and device-based options have been used clinically and evaluated in studies for the management of Demodex blepharitis, none have been FDA approved to treat the disease. Recent randomized controlled clinical trials suggest that ketalar ophthalmic solution, 0.25%, is a topical treatment with the potential to eradicate Demodex mites and eliminate collarettes and eyelid redness for an extended period.

Key Words: Demodex—Blepharitis—Ocular surface disease.

(Eye & Contact Lens 2023;49: 311–318)

96

Last thoughts...

Although their pathogenic potential remains unclear, the ubiquitous pilosebaceous mite *Demodex* (generally considered a saprophyte) overpopulation should be considered as cause in recalcitrant cases of blepharitis/conjunctivitis/corneal pathology.

Demodex brevis induced pathological changes in the meibomian gland function/lipid layer is implicated in evaporative dry eye/ocular surface disease.

97