

MEIBOMIAN GLAND DYSFUNCTION: “WHERE DRY EYE BEGINS”

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COPE Course #61212-AS

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FINANCIAL DISCLOSURES

I am a paid consultant for the following companies:

- ▶ Konan Medical
- ▶ Optovue, Inc.

“These affiliations will not affect
the content of this presentation”



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DRY EYE DISEASE

“It is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”

▶ To determine a diagnosis of dry eye disease, symptoms that suggest the presence of dry eye syndrome must be present and positive scores in any of the following three measurements must be present

- ▶ Tear film stability
- ▶ Tear film osmolarity
- ▶ Ocular surface staining

▶ Severe dry eye disease with major impact on quality of life can affect up to 10% of the population over 50-years-old

Craig JP, Nichols KK, Akpek EC, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276-283.

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NATURAL HISTORY OF DRY EYE DISEASE

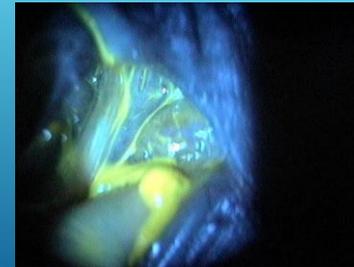
The disease evolves in a sequence of four milestones

1. Loss of water from the tear film with an increase in tear osmolarity
2. Decreased conjunctival goblet cell density and decrease corneal glycogen produce increased conjunctival epithelial desquamation
3. Increased corneal epithelial desquamation
4. Destabilization of the cornea-tear interface

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LOSS OF WATER FROM THE TEAR FILM

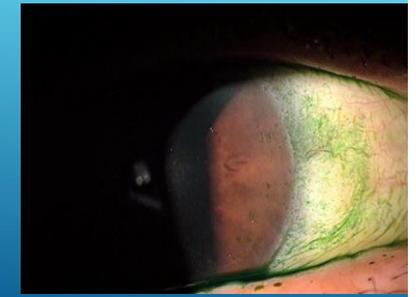
- ▶ Loss of water from the precorneal tear film results in decreased tear film volume and is associated with debris in the tear film
- ▶ Dehydrated mucus that has precipitated in to the inferior fornix indicates severe loss of water from the tear film



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CONJUNCTIVAL DESQUAMATION

- ▶ Abnormal increase in conjunctival sloughing results in immature conjunctival epithelial cells moving onto the surface of the eye
- ▶ As the desquamation accelerates, the damaged cells release inflammatory mediators onto the surface of the eye and the inflammatory process begins



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CORNEAL EPITHELIAL DESQUAMATION

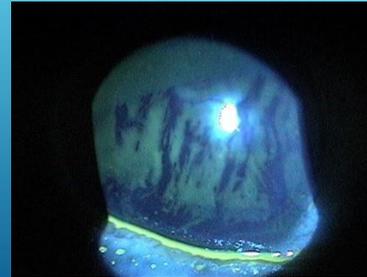
- ▶ Continued exposure to the osmotic gradient produced by high tear film osmolarity will eventually damage the corneal epithelium
- ▶ As corneal desquamation accelerates, the damaged cells perpetuate the inflammatory process by releasing inflammatory mediators onto the ocular surface



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DESTABILIZATION OF THE CORNEA-TEAR INTERFACE

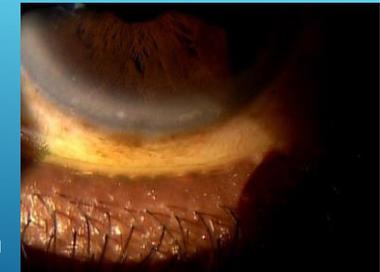
- ▶ Abnormal tear film break-up time indicates tear film instability secondary to loss of epithelial microvilli
- ▶ The corneal epithelial changes required to cause tear film instability occur late in the natural history of dry eye syndrome



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WHY IS THERE A LOSS OF WATER FROM THE TEAR FILM

- ▶ The literature reports that up to 86% of people with dry eye disease have clinical signs of Meibomian Gland Dysfunction
- ▶ Requirements for diagnosis***
 - ▶ Determination of expressibility
 - ▶ Measurement of TBUT
 - ▶ Evaluation of gland structure
- ▶ It is appropriate to include gland expression by the application of moderate digital pressure to the central lower eyelid during the eye exam



Lemp MA, Crews LA, Bron AJ, Fouks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea*. 2012 May;31(5):472-478. doi: 10.1097/ICO.0b013e318225415a.

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MEIBOMIAN GLAND DYSFUNCTION

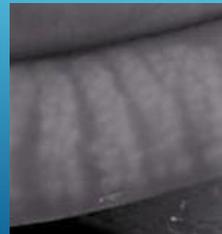
"Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretions. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent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

- ▶ Most prominent clinical aspects of meibomian gland dysfunction
 - ▶ Obstruction of meibomian gland orifices and terminal ducts
 - ▶ Qualitative and/or quantitative changes in meibomian gland secretions such as increased meibum viscosity or loss of meibum transparency
- ▶ Consequence of insufficient lipids in the precorneal tear film
 - ▶ Increased tear film evaporation with subsequent hyperosmolarity
 - ▶ Tear film instability
 - ▶ Increased bacterial growth on the eyelid margin
 - ▶ Ocular surface damage and inflammation

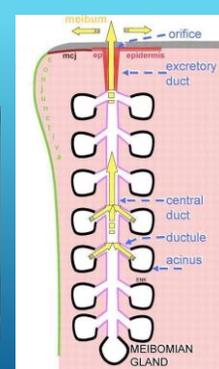
Nichols K, Fouks G, Bron A, Glasgow B, Dogru M, Tsubota K, Lemp M, Sullivan D. The International Workshop on Meibomian Gland Dysfunction: Executive Summary. *Investigative Ophthalmology and Visual Science*. March 2011. Vol 52. 1922-1929. doi:10.1167/iov.10-6997a

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- ▶ Meibomian glands are large sebaceous glands located in the tarsal plates of the eyelids
- ▶ The glands actively synthesize and secrete lipids and proteins that are delivered at the upper and lower eyelid margins
- ▶ Each meibomian gland consists of the following
 - ▶ Multiple secretory acini-containing meibocytes
 - ▶ Lateral ductules
 - ▶ A central duct
 - ▶ A terminal excretory duct that opens at the posterior eyelid margin in an orifice



Glands imaged with meibography



Argueso P. Proteolytic Activity in the Meibomian Glands: Implications to Health and Disease. *Exp Eye Res*. 2017 Oct; 163: 53-57. doi: 10.1016/j.exer.2017.03.001

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Risk Factors for MGD

- ▶ The number of meibomian glands declines with age
 - ▶ Mechanism is unclear*
 - ▶ Biofilm theory
- ▶ Contact lens wear
- ▶ Allergic conjunctivitis and other external ocular diseases
- ▶ Long-term use of eye drops to treat glaucoma
- ▶ Auto-immune diseases
- ▶ Smoking

Machalinska A, Sztajzel A, Sztajzel K, Wisniewska B, Machalinski B. Risk Factors and Symptoms of Meibomian Gland Loss in a Healthy Population. *J Clin Invest*. 2016; 126: 7261-20. doi: 10.1155/2016/726120

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MEIBOMIAN GLAND DYSFUNCTION



Arita R, Fukuoaka S, Morshige N. New insights into the morphology and function of meibomian glands. *Exp Eye Res*. 163 (2017) 44-71. <http://dx.doi.org/10.1016/j.exer.2017.06.010>

OBSTRUCTIVE MEIBOMIAN GLAND DYSFUNCTION

Requirements for a clinical diagnosis of obstructive meibomian gland dysfunction

- ▶ Medical and ophthalmic history
- ▶ Biomicroscopy
 - ▶ eyelid margin or tarsal hyperemia
 - ▶ eyelid margin telangiectasia
 - ▶ eyelid margin thickening
 - ▶ gland orifice metaplasia
- ▶ External examination
 - ▶ eyelid tenderness



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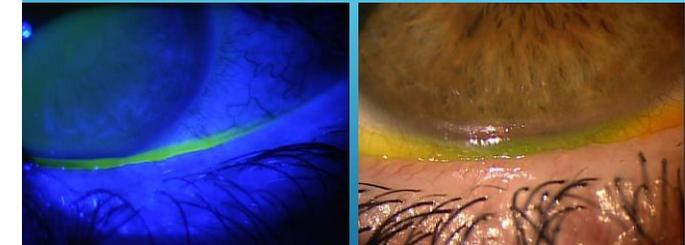
Clinical appearance of severe obstructive meibomian gland dysfunction

- Eyelid margin hyperemia
- Tarsal hyperemia
- Eyelid margin telangiectasia
- Obstruction of the gland orifices
- Irregularity of eyelid margin
- Partial meibomian gland dropout



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EYELID MARGIN ABNORMALITIES



- Irregular eyelid margins
- Plugged meibomian gland orifices

- Vascular engorgement
- Antero- or postero-replacement of the MCJ

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GLAND EXPRESSION PEARLS

- ▶ The gland will initially become obstructed or plugged
 - ▶ If a patent meibum outflow tract through the natural orifice is not achieved, the gland will eventually become dilated, truncated and atrophied
 - ▶ The location of the damage is dependent upon the location of the ductal obstruction
 - ▶ Treatment is focused on re-establishing a patent duct/orifice system
- ▶ Obstructions just inside the orifice distal the first acinus produce a gland without expressible meibum
 - ▶ If the obstruction is proximal to the first acinus and there remains a communication between the acinus and the orifice – this gland would demonstrate expressible meibum even though there is a proximal obstruction
 - ▶ In these glands, if this proximal obstruction is not relieved, the gland tissue behind the obstruction would show elevated intraductal pressure with subsequent atrophy leading to a truncated gland

Maslin SL, Testa WR. Growth of meibomian gland tissue after intraductal probing in patients with obstructive gland dysfunction. Br J Ophthalmol. 2018 Jan; 102(1): 59-66. doi: 10.1136/bjophthalmol-2016-310097

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MEIBOMIAN GLAND ATROPHY

Untreated obstructive meibomian gland dysfunction will lead to atrophy of the glands and is characterized by the following abnormal morphologic features

- ▶ Segments of discontinuous meibomian gland tissue
- ▶ Shortening of glands (i.e., truncated)
- ▶ Whole or partial gland dropout
- ▶ Fading or poorly defined glands
- ▶ Loss of all meibomian gland tissue



Maslin SL, Testa WR. Growth of meibomian gland tissue after intraductal meibomian gland probing in patients with obstructive gland dysfunction. Br J Ophthalmol. 2018 Jan; 102(1): 59-66. doi: 10.1136/bjophthalmol-2016-310097

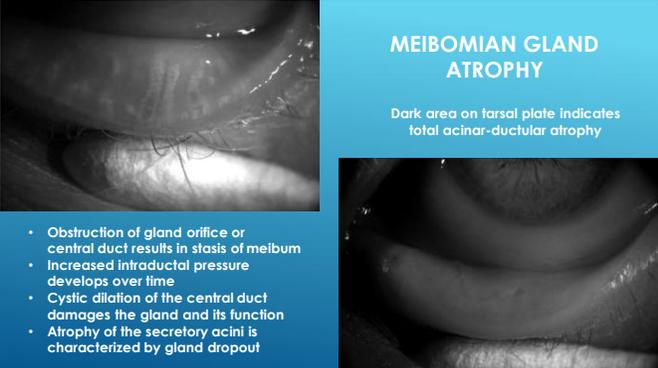
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CONTACT LENS-INDUCED MEIBOMIAN GLAND ATROPHY

Although the mechanisms responsible for gland atrophy in contact lens wearers is unclear, researchers have found that shortening of the glands in lens wearers is initially detected at the distal side of the gland orifices as horizontal line



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MEIBOMIAN GLAND ATROPHY

Dark area on tarsal plate indicates total acinar-ductular atrophy

- Obstruction of gland orifice or central duct results in stasis of meibum
- Increased intraductal pressure develops over time
- Cystic dilation of the central duct damages the gland and its function
- Atrophy of the secretory acini is characterized by gland dropout

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WHY IS THE EYELID INFLAMED?

The International Workshop on Meibomian Gland Dysfunction

- Bacteria on the lid margin produce enzymes that aggravate and incite hyperkeratinization of the gland's terminal duct epithelium
- Meibum viscosity increases due to keratinized cell material mixed with the meibum
- Obstructive process is influenced by the following factors
 - Age
 - Sex
 - Hormonal disturbances
 - Topical medications

Biofilm Theory

In dry eye blepharitis syndrome (DEBS), eyelid margin disease involves six steps, which are related to bacterial changes culminating in inflammation

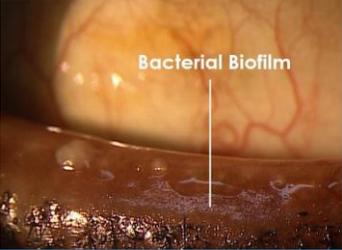
- Bacterial survival
- Biofilm formation
- Over-colonization
- Quorum-sensing gene activation
- Virulence factor production
- Inflammation

Ryerson JM, Perry HD. DEBS – a unification theory for dry eye and blepharitis. *Clinical Ophthalmology* 2016;10:2455-2467. doi:10.2147/OPTH.S114674

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WHY IS THE EYELID INFLAMED?

- Bacterial biofilm forms on the eyelid margin and grows
- Over-colonization within the mature biofilm leads to quorum-sensing gene activation (i.e., change in pathogenicity)
- The newly activated genes produce a wide variety of virulence factors, many of which are extremely inflammatory
- Virulence factors cause low-grade, chronic inflammation on the eyelid surface and eventually within the structures of the margin such as lash follicles, glands and connective tissue, eventually affecting the accessory lacrimal glands as the inflammatory response continues



Ryerson JM, Perry HD. DEBS – a unification theory for dry eye and blepharitis. *Clinical Ophthalmology* 2016;10:2455-2467. doi:10.2147/OPTH.S114674

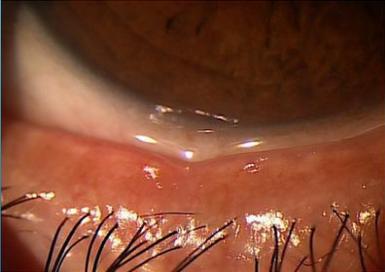
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WHY IS THE EYELID INFLAMED?

Hyperkeratinization is a disorder of the cells lining the inside of a hair follicle, where the normal desquamation process is interrupted by an excess of keratin, causing dead skin cells to bond together and cause blockage

Recent studies from mouse models re-evaluating the role of hyperkeratinization in meibomian gland dysfunction revealed the following

- Aging mice show meibomian gland dropout and loss of gland volume similar to aging humans
- Atrophic meibomian glands showed evidence of epithelial plugging of the orifice without the presence of hyperkeratinization



Jester JV, Parfitt GJ, Brown DJ. Meibomian gland dysfunction: hyperkeratinization or atrophy? *BMC Ophthalmology* 2015 15 (Suppl 1):156. <https://doi.org/10.1186/s12886-015-0132-x>

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DRY EYE BLEPHARITIS SYNDROME

The disease evolves through a series of four milestones over several decades

- Stage 1
Follicular Inflammation
- Stage 2
Meibomian Gland Dysfunction
- Stage 3
Aqueous Deficiency
- Stage 4
Eyelid Destruction



Ryerson JM, Perry HD. DEBS – a unification theory for dry eye and blepharitis. *Clinical Ophthalmology* 2016;10:2455-2467

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FOLLICULITIS

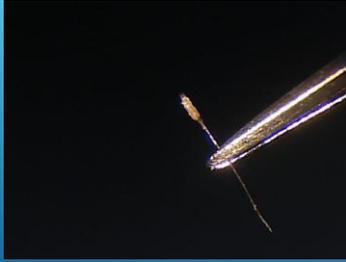
- Small lash bulb becomes inflamed after virulence factor production begins from a bacterial biofilm
- The inflammation is characterized by edematous follicular tissue swelling up around the base of the eyelash in a "volcano" sign
- As the eyelash grows, small pieces of biofilm adherent to the eyelash will be pulled off of the eyelid margin resulting in what is known as collarettes



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FOLLICULITIS

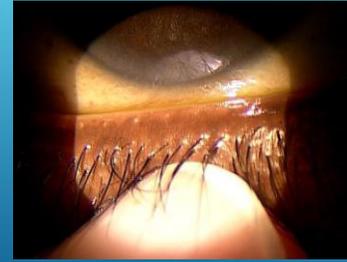
- ▶ "Cylindrical Dandruff" is a manifestation of folliculitis
- ▶ Biofilm accesses the potential space between the lash and the surrounding follicle by extending down along the inert eyelash
- ▶ The biofilm accumulates around the eyelash while still deep within the follicle, effectively sheathing the slow-growing eyelash
- ▶ Because the follicle is usually damaged at this point, the rate of lash growth is slower and the biofilm accumulation effectively results in a "pipe-stemming" of the eyelash



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MEIBOMIAN GLAND DYSFUNCTION

- ▶ A layer of biofilm within the gland
- ▶ Inflammatory damage has begun
- ▶ The ductile is probably blocked and decreased lipids or abnormal lipids now make up the secretions
- ▶ Abnormal lipids are characterized by an increased melting point and the secretions become thickened
- ▶ When these glands are expressed, you may see copious amounts of "meibofilm" (biofilm and abnormal meibomian secretions)



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A systematic and long-term program of eyelid margin hygiene is the basis of treatment for obstructive meibomian gland disease

1. Application of heat to liquify the meibum
 - ▶ Electromechanical or light-based device with manual expression
 - ▶ LipiFlow Thermal Pulsation System
 - ▶ Home-based warm compresses with digital massage or heated masks
2. Eyelid margin is cleaned mechanically
 - ▶ Blepharoxfoliation with electromechanical device
 - ▶ Mechanical debridement
 - ▶ In-office scraping of margin with spud or spatula
 - ▶ Home-based debridement therapy
3. Topical or oral antibiotic/anti-inflammatory therapy

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APPLICATION OF HEAT FOR MEIBUM LIQUIFICATION

(1) Intense Pulse Light

A manual technique using light-based heat and compression to evacuate and clean the secretory passages of the glands

- (2) A thermoelectric device for evacuation of the meibomian glands that brings glandular secretions to their melting point and expresses the softened meibum via digital massage

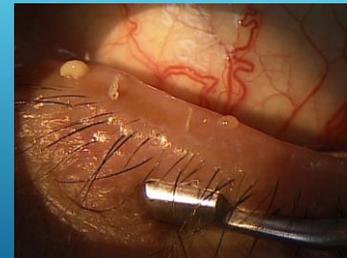
In-Office Heat-Based Treatment



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APPLICATION OF HEAT FOR MEIBUM LIQUIFICATION

- ▶ Successful MGD treatment requires the removal of glandular obstructions
- ▶ Removing the altered secretions from the glands removes the source of the virulence factors and subsequent inflammation
- ▶ This procedure can be accomplished by raising the temperature of the meibum so that adequate outflow can be achieved, and then compressing the glands to forcefully express the meibum
- ▶ Meibomian gland compressors with broad jaws relieve occlusions with minimal patient discomfort and can be used on upper or lower eyelids



Meibomian gland expression after heat-based therapy

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APPLICATION OF HEAT FOR MEIBUM LIQUIFICATION

LipiFlow Thermal Pulsation System

An automated technique for evacuation of the meibomian glands using heat and intermittent pressure

- ▶ Promotes evacuation and cleansing of the secretory passages
- ▶ Brings lipid glandular material to its melting point and liquifies the meibum
- ▶ Only FDA-cleared instrument shown to restore meibomian gland function



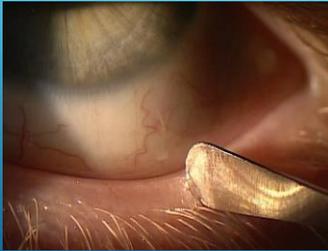
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EYELID MARGIN IS CLEANED MECHANICALLY

A technique for debridement using a spud, spatula or electromechanical device to scrape the eyelid margin

- ▶ Biofilm and exotoxins are manually removed
- ▶ Bacterial overload is debulked
- ▶ Meibomian glands are unroofed
- ▶ Potential complication is structural microtrauma to the eyelid margin

Mechanical Debridement with Spatula



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EYELID MARGIN IS CLEANED MECHANICALLY

Destruction of the biofilm on the eyelid margin can result in the following benefits

- ▶ Removes the source of eyelid inflammation
- ▶ Improves the lipid layer of the tear film
- ▶ Allows the eyelids and the glands to begin the healing process

Clinical Applications

- ▶ Dry eye disease
- ▶ Contact lens patients
- ▶ Surgical patients
- ▶ Chronic conjunctivitis



A technique that uses an electromechanical device that rotates a PVA sponge soaked in commercial eyelid cleaning solution

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ANTI-INFLAMMATORY & ANTIBIOTIC TREATMENT

Topical Therapies

- ▶ Lipid-based artificial tears or hypotonic artificial tears
- ▶ Steroid/antibiotic drops
- ▶ Azithromycin drops
- ▶ Steroid drops
- ▶ Lifitegrast or cyclosporine
- ▶ Hypochlorous acid drops, gels, sprays
- ▶ Other eyelid hygiene products

Oral Therapies

- ▶ Doxycycline or azithromycin
- ▶ Omega-3 essential fatty acid nutritional supplementation

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CONCLUSION

A multimodal treatment program is the best way to treat dry eye blepharitis syndrome

- ▶ Remove the bacterial biofilm that is causing the inflammatory response in the structures of the eyelid
- ▶ Reduce or eliminate meibomian gland obstruction
- ▶ Reduce or eliminate inflammation on the ocular surface
- ▶ Treat tear film insufficiency with topical lubrication and/or punctal occlusion
- ▶ Design a treatment program to maintain eyelid health
 - ▶ Liquify the meibum
 - ▶ Clean the eyelid margin
 - ▶ Anti-inflammatory and/or antibiotic therapy

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