UNIVERSITY of HOUSTON
HEALTH AND BIOMEDICAL SCIENCES CENTER

EU Regulatory Workshop: Meibomian Gland Dysfunction

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Disclosures

- K. Nichols
  - Paid consultant to:
    - Alcon
    - Allergan
    - Celtic/ Resolvyx
    - Eleven Biotherapeutics
    - InSite
    - Ista
    - SARcode
    - TearLab
- Research support
  - CL Tear Film Lab (OSU)
    - Alcon
    - CIBA
    - Inspire
    - TearLab
    - Pfizer
    - Vistakon
  - National Eye Institute
    - R01 EY015519 (PI)
    - R01 EY017951 (Co-I)
    - R34 EY017626 (Co-I)

MGD Contributes to Dry Eye

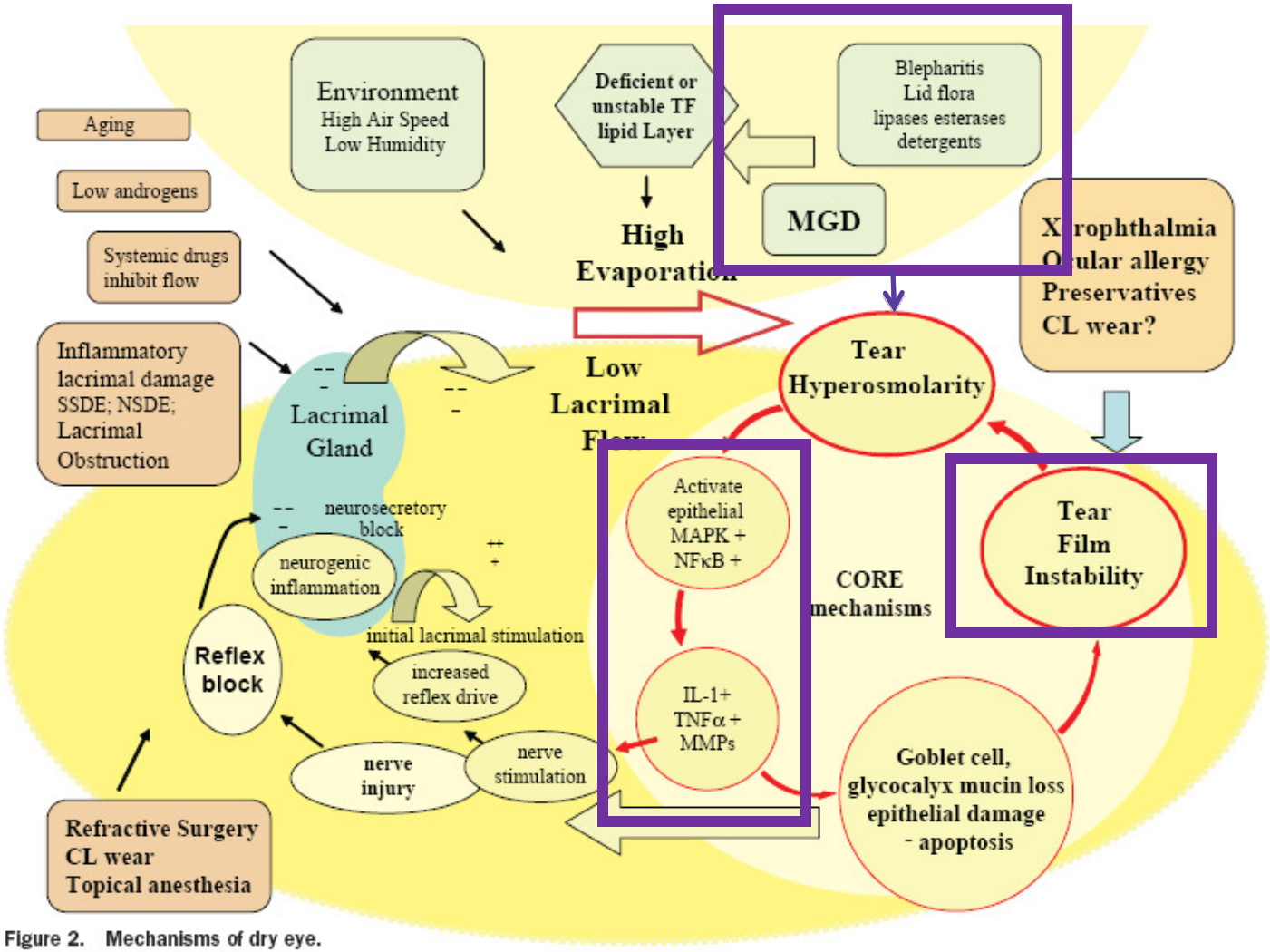


Figure 2. Mechanisms of dry eye.

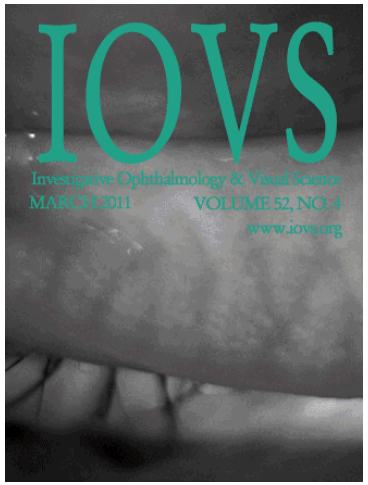
DEWS Definition and classification report. *Ocular Surface* 2007

Table 2. Dry eye severity grading scheme

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic occurs under environ stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying, chronic and/or constant limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/–	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

*Must have signs AND symptoms. TBUT: fluorescein tear break-up time. MGD: meibomian gland disease

Reprinted with permission from Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. *Cornea* 2006;25:90-7



TFOS International MGD Workshop

Special Issue

The International Workshop on Meibomian Gland Dysfunction: Executive Summary

Kelly K. Nichols,[1] Gary N. Foulks,[2] Anthony J. Bron,[3] Ben J. Glasgow,[4,5] Murat Dogru,[6] Kazuo Tsubota,[6] Michael A. Lemp,[7] and David A. Sullivan[8,9]

- Over 65 International clinicians, scientists, and industry participants
- 2+ year process
- Published in March 2011, *IOVS*
- #1 Most downloaded *IOVS* article for the last 12 months
- Downloaded over 5500 times
- All MGD workshop reports are in the "top 10"
- Translation into 12 languages
- www.tearfilm.org

The 65 Most-Frequently Read Articles
in Invest. Ophthalmol. Vis. Sci. during **October 2010 thru September 2011** -- updated monthly

Most-read rankings are recalculated at the beginning of the month and are based on full-text and pdf views.

1. Kelly K. Nichols, Gary N. Foulks, Anthony J. Bron, Ben J. Glasgow, Murat Dogru, Kazuo Tsubota, Michael A. Lemp, David A. Sullivan
The International Workshop on Meibomian Gland Dysfunction: Executive Summary
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 1922-1929.
(In "Special Issue") [Full Text] [PDF]
(Read 5554 times)

2. Kelly K. Nichols
The International Workshop on Meibomian Gland Dysfunction: Introduction
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 1917-1921.
(In "Special Issue") [Full Text] [PDF]
(Read 5318 times)

3. Erich Knop, Nadja Knop, Thomas Millar, Hiroto Obata, David A. Sullivan
The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Anatomy, Physiology, and Pathophysiology of the Meibomian Gland
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 1938-1978.
(In "Special Issue") [Full Text] [PDF]
(Read 4663 times)

4. Alan Tomlinson, Anthony J. Bron, Donald R. Korb, Shiro Amano, Jerry R. Paugh, E. Ian Pearce, Richard Yee, Norihiko Yokoi, Reiko Arita, Murat Dogru
The International Workshop on Meibomian Gland Dysfunction: Report of the Diagnosis Subcommittee
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 2006-2049.
(In "Special Issue") [Full Text] [PDF]
(Read 4074 times)

5. Gerd Geerling, Joseph Tauber, Christophe Baudouin, Eiki Goto, Yukihiro Matsumoto, Terrence O"Brien, Maurizio Rolando, Kazuo Tsubota, Kelly K. Nichols
The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Management and Treatment of Meibomian Gland Dysfunction
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 2050-2064.
(In "Special Issue") [Full Text] [PDF]
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6. J. Daniel Nelson, Jun Shimazaki, Jose M. Benitez-del-Castillo, Jennifer P. Craig, James P. McCulley, Seika Den, Gary N. Foulks
The International Workshop on Meibomian Gland Dysfunction: Report of the Definition and Classification Subcommittee
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 1930-1937.
(In "Special Issue") [Full Text] [PDF]
(Read 3221 times)

7. Penny A. Asbell, Fiona J. Stapleton, Kerstin Wickström, Esen K. Akpek, Pasquale Aragona, Reza Dana, Michael A. Lemp, Kelly K. Nichols
The International Workshop on Meibomian Gland Dysfunction: Report of the Clinical Trials Subcommittee
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 2065-2085.
(In "Special Issue") [Full Text] [PDF]
(Read 2580 times)

8. Kari B. Green-Church, Igor Butovich, Mark Willcox, Douglas Borchman, Friedrich Paulsen, Stefano Barabino, Ben J. Glasgow
The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Tear Film Lipids and Lipid–Protein Interactions in Health and Disease
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 1979-1993.
(In "Special Issue") [Full Text] [PDF]
(Read 2546 times)

9. Debra A. Schaumberg, Jason J. Nichols, Eric B. Papas, Louis Tong, Miki Uchino, Kelly K. Nichols
The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on the Epidemiology of, and Associated Risk Factors for, MGD
Invest Ophthalmol Vis Sci Mar 30, 2011; 52: 1994-2005.
(In "Special Issue") [Full Text] [PDF]
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Tfos Scientific Reports

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MGD REDEFINED: INTERNATIONAL WORKSHOP ON MEIBOMIAN GLAND DYSFUNCTION REPORT AVAILABLE

Report Overview, Link to Full Report & Press Release

BOSTON, MA, March 31, 2011-

The Tear Film & Ocular Surface Society (TFOS) reported the conclusions and recommendations of the International Workshop on Meibomian Gland Dysfunction (MGD).

The MGD Workshop, sponsored by TFOS, was conducted to provide an evidence-based evaluation of meibomian gland structure and function in health and disease. MGD is an extremely important condition, conceivably underestimated, and very likely the most frequent cause of dry eye disease.

The Report required over 2 years to complete and involved the efforts of more than 50 leading clinical and basic research experts from around the world.

- Report Overview
- Link to full Report (IOVS)
- Press Release
- In the press

NEWS & EVENTS

- **Dry Eye Review Blog:. Industry Experts blogging about Dry Eye Disease**

subscribe now!or view entries!

- **TFOS Meibomian Gland Dysfunction Report online**

TFOS MGD Report available now

- **The 6th International Conference on the Tear Film & Ocular Surface**

Basic Science and Clinical Relevance
Abstract Book, Highlights & Historical Perspective

Anatomy, Physiology and Pathophysiology of the Meibomian Gland

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

Erich Knop, M.D., Ph.D. (Chair)
Nadja Knop, M.D., Ph.D.
Thomas J. Millar, Ph.D.
Hiroto Obata, M.D.
David A. Sullivan, Ph.D.

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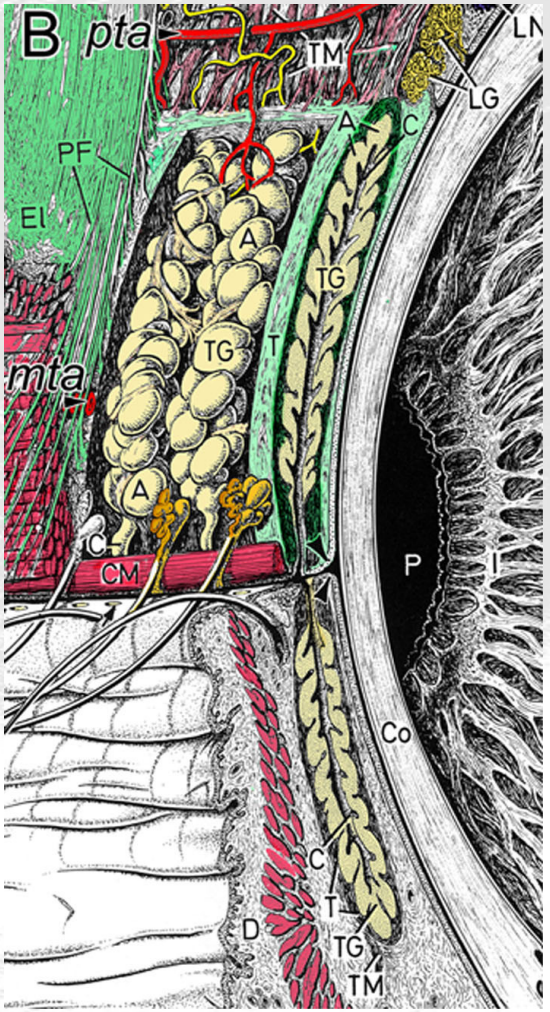
Meibomian Gland - ANATOMY

- Large sebaceous glands
- No direct contact to hair follicles
- Located in the tarsal plates
  - Upper and lower eye lids



Modified and colored from Krstic H. Human microscopic anatomy. Springer Medizin Verlag 1991, (reproduced from Knop N & Knop E Ophthalmologe 2009; 106:872–883)

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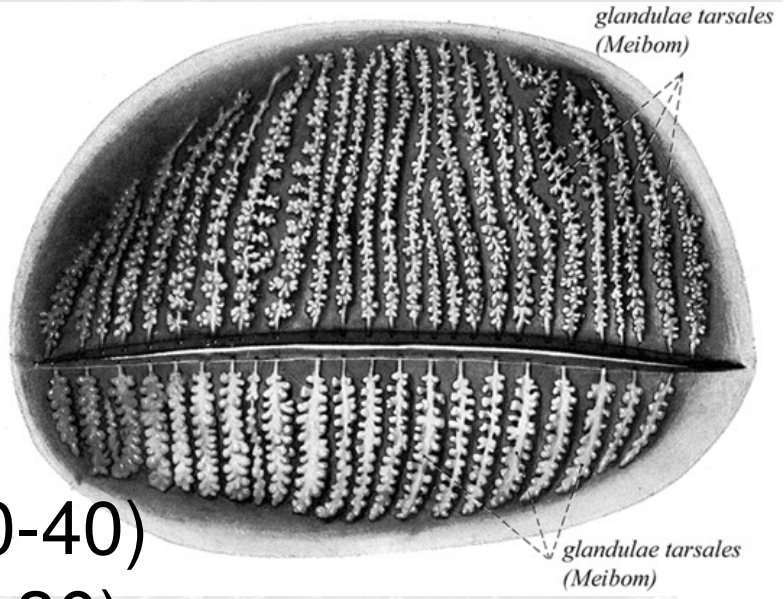
Meibomian Gland - ANATOMY



Modified from Sobotta Atlas der Anatomie des Menschen. Urban & Schwarzenberg Verlag 1982, (reproduced from Knop N & Knop E. Ophthalmologe 2009; 106:872–883)

- **Length**
  - Follows the tarsus
- **Number**
  - More in upper lid (30-40)
  - Less in lower lid (20-30)
- **Volume**
  - Higher in upper lid (26µl vs. 13µl)
- Relative functional contribution (upper vs. lower) to the tear film lipid layer is unknown

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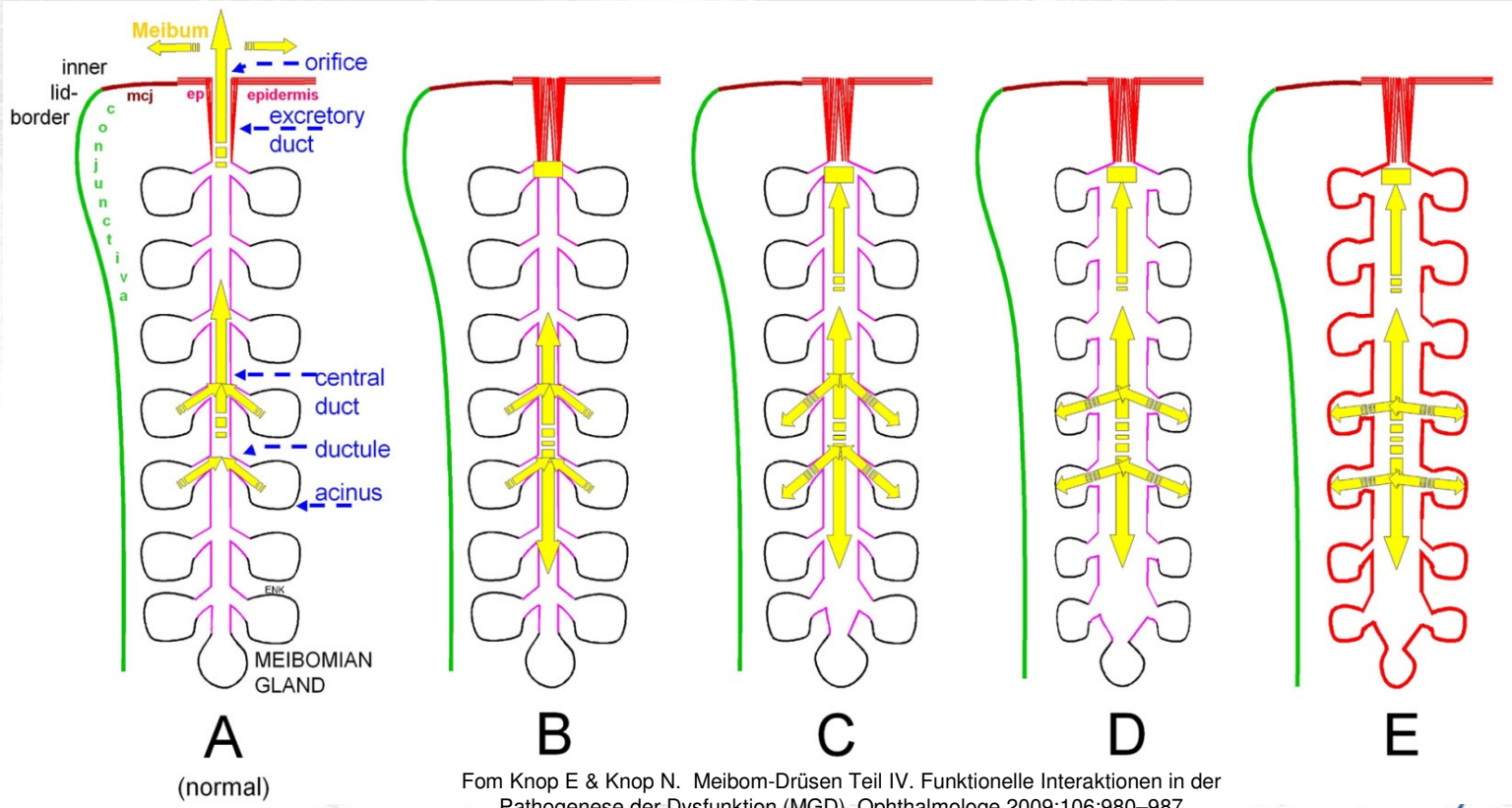
Meibomian Gland – PATHOLOGY

- Obstructive PCT leads to a progressive ductal DILATATION and acinar ATROPHY



Fom Knop E & Knop N. Meibom-Drüsen Teil IV. Funktionelle Interaktionen in der Pathogenese der Dysfunktion (MGD). Ophthalmologe.2009;106:980–987

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Interacting Pathways in

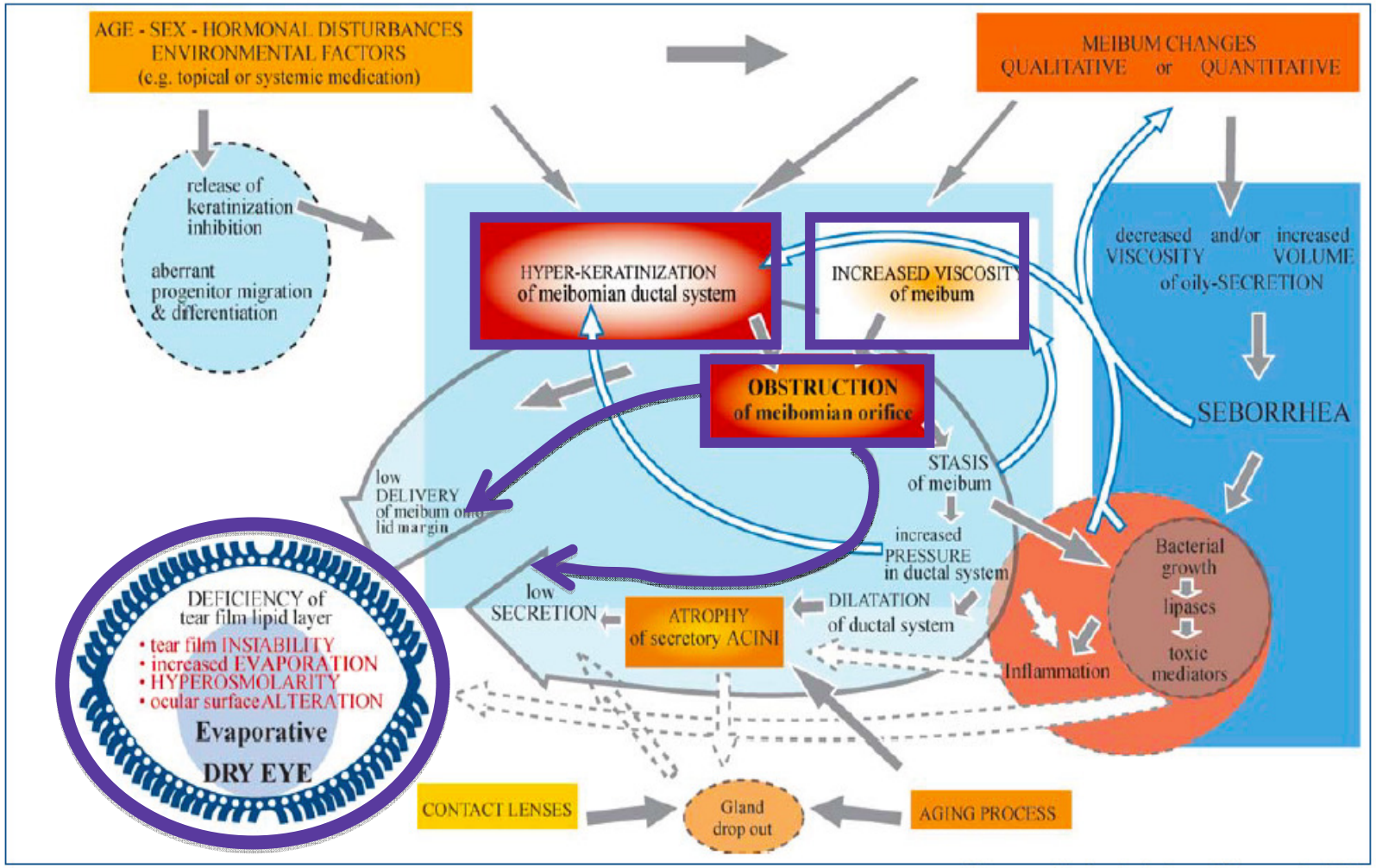

Figure 2. *Pathophysiology of obstructive MGD*

Modified from Knop E & Knop N. Meibom-Drüsen Teil IV. Funktionelle Interaktionen in der Pathogenese der Dysfunktion (MGD). Ophthalmologe.2009;106:980–987

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Meibomian Gland Dysfunction Definition & Classification

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

J. Daniel Nelson, M.D. (Co-Chair)
Jun Shimazaki, M.D., Ph.D. (Co-Chair)
Jose M. Benitez-del-Castillo, M.D., Ph.D.
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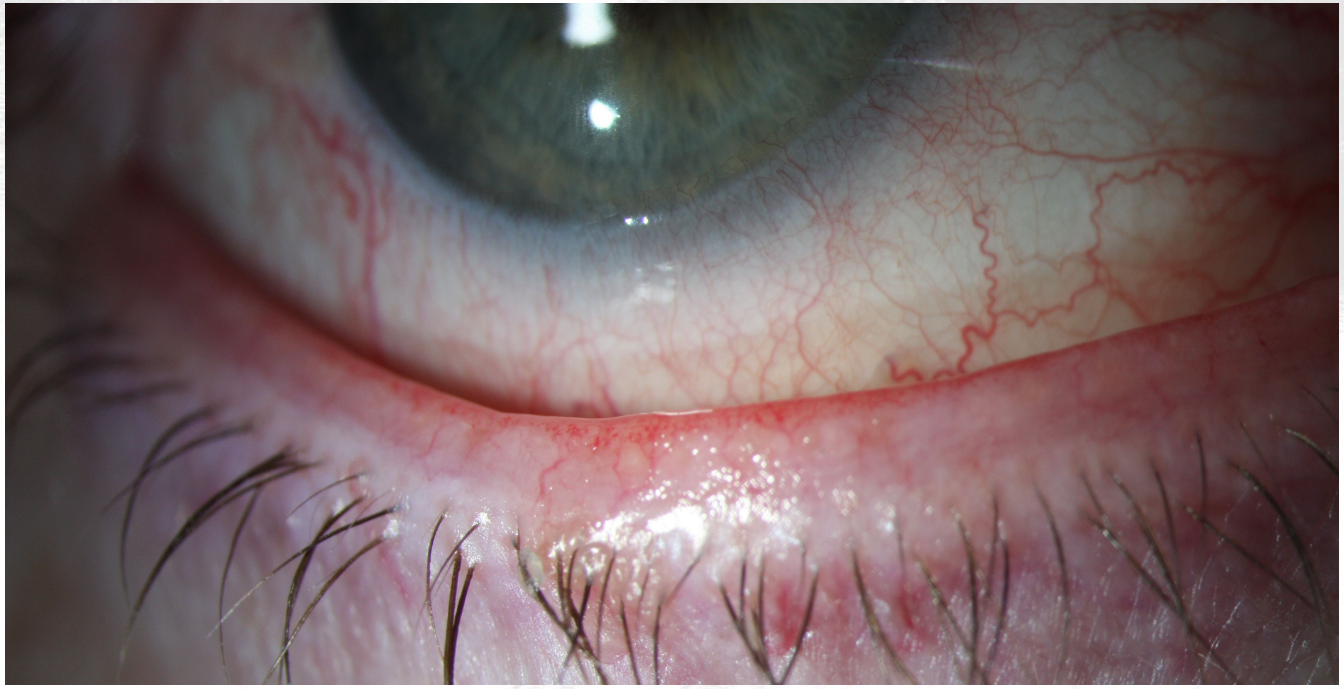
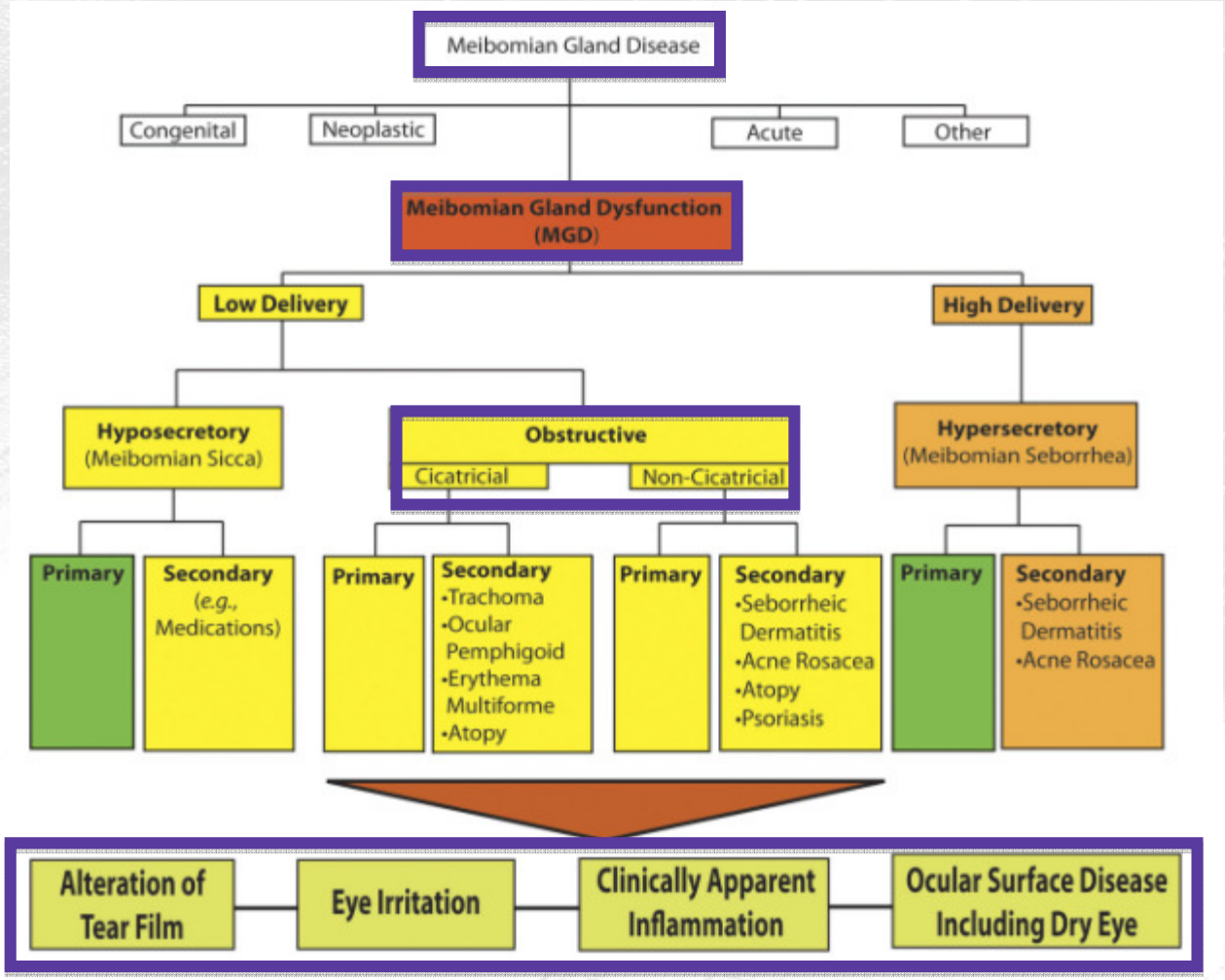
What is MGD?

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.



Classification of MGD



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Epidemiology and Associated Risk Factors of Meibomian Gland Dysfunction

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

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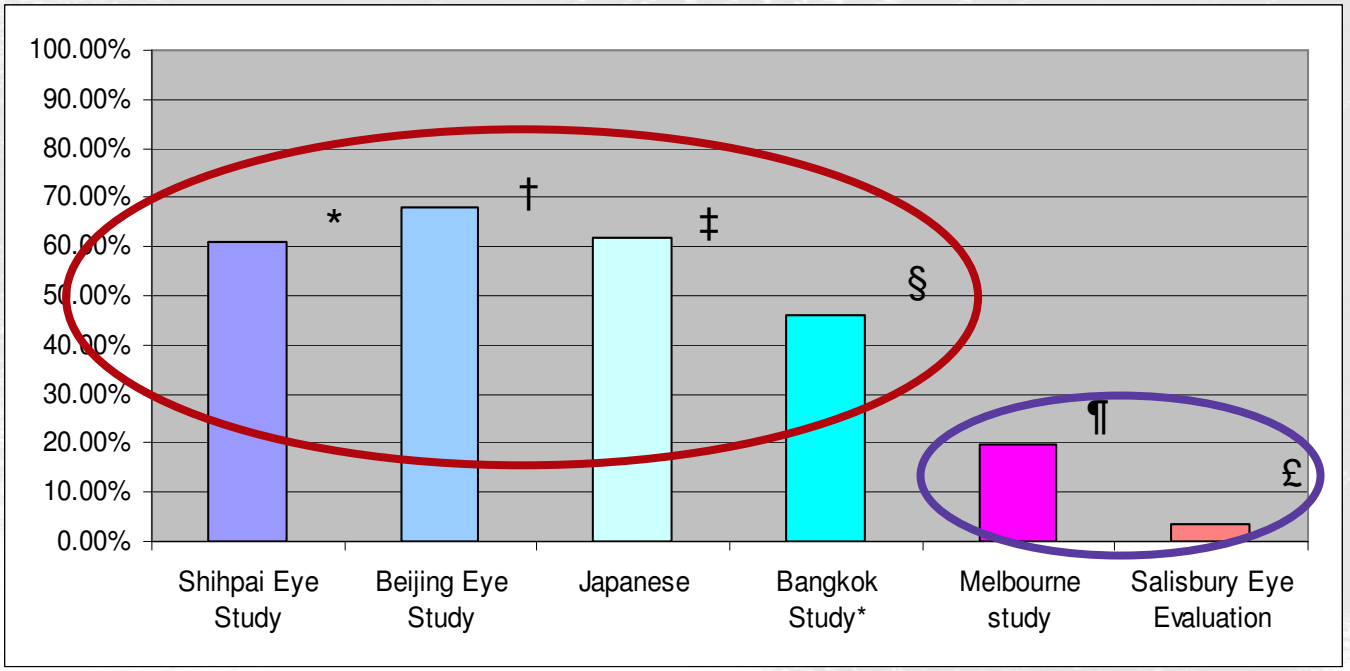
Prevalence of MGD



* Telangiectasia or Meibomian gland orifice plugging

† Telangiectasia

‡ Gland dropout, expressibility and nature of Meibum secretion

§ Telangiectasia or Meibomian gland orifice plugging OR collarettes

¶ Tear break up time < 1SD (10 sec)

£ Meibomian gland plugging OR collarettes (grade 2-3)

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Factors Associated with MGD

Special Issue

The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on the Epidemiology of, and Associated Risk Factors for, MGD

Debra A. Schaumberg,[1] Jason J. Nichols,[2] Eric B. Papas,[3] Louis Tong,[4] Miki Uchino,[5] and Kelly K. Nichols[2]

Factor	Reference
Aniridia	Jastaneiah and Al-Rajhi[48]
Chronic blepharitis (anterior or posterior)	Auw-Haedrich and Reinhard[40] Jackson[38] Mathers et al.[37] McCulley et al.[39] McCulley and Shine[49]
Contact lens wear	Arita et al.[36] Marren[33] Molinari and Stanek[34] Ong and Larke[32]
Demodex folliculorum	Czepita et al.[50] Kheirkhah et al.[51]
Eyelid tattooing	Kojima et al.[52]
Floppy eyelid syndrome	Gonnering and Sonneland[53]
Giant papillary conjunctivitis	Mathers and Billborough[54] Martin et al.[55] Molinari and Stanek[34]
Ichthyosis	Baden and Imber[56]
Salzmann's nodular corneal degeneration	Farjo et al.[57]
Trachoma	Bron and Tiffany[58]

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Factors Associated with MGD

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TABLE 5. Systemic Factors Hypothesized to Correlate with MGD

Factor	Reference
Aging	Den et al.[62]
	DEWS[46]
	Hykin and Bron[63]
	Schaumberg et al.[70]
	Schaumberg et al.[71]
	Sullivan et al.[64]
Androgen deficiency	Krenzer et al.[72]
	Sullivan et al.[73]
	Sullivan et al.[65]
Atopy	Bron et al.[15]
Benign Prostate Hyperplasia	Schaumberg et al.[70]
Cicatricial pemphigoid	Bron and Tiffany[58]
Complete androgen-insensitivity syndrome	Cermak et al.[74]
	Sullivan et al.[75]
Discoid lupus erythematosus	Ena et al.[76]
Ectodermal dysplasia syndrome	Kaercher[77]
Hematopoietic stem cell transplantation	Ogawa et al.[78]
Hypertension	Schaumberg et al.[70]
Menopause*	Mathers et al.[66]
	Sullivan et al.[65]
Parkinson's Disease	Tamer et al.[79]
Pemphigoid	Iovine et al.[80]
Polycystic ovary syndrome	Yavas et al.[81]
Psoriasis	Horwath-Winter et al.[82]
	Zengin et al.[83]
Rosacea	Akpek et al.[84]
	Alvarenga and Mannis[85]
	Zengin et al.[86]
	Zuber[87]
	Zuber[88]
Sjögren's syndrome	Goto et al.[68]
	Krenzer et al.†
	Pflugfelder et al.[69]
	Shimazaki et al.[43]
	Sullivan et al.[65]
	Sullivan et al.[89]
Stevens-Johnson syndrome	Sotozono et al.[90]
Toxic epidermal necrolysis	Di Pasquale et al.[91]
	Sotozono et al.[90]
Turner syndrome	Bron and Tiffany[58]

Factors Associated with MGD

Special Issue

The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on the Epidemiology of, and Associated Risk Factors for, MGD

TABLE 6. Medications Hypothesized to Correlate with MGD

Medication	Reference
Isotretinoin (13-*cis* retinoic acid) therapy*	Caffery and Josephson[94] Egger et al.[95] Mathers et al.[95]
Antiandrogens	Krenzer et al.[72] Sullivan et al.[73] Sullivan et al.[65]
Antidepressants	Chia et al.[96] Moss et al.[97] Schaumberg et al.[70]
Antihistamines	Moss et al.[97] Ousler et al.[98]
Medications used to treat benign prostate hyperplasia	Schaumberg et al.[70]
ω-3 Fatty acids (possibly protective)	Barabino et al.[99] Creuzot et al.[100] Kokke et al.[101] Macsai[102] Miljanović et al.[103] Pinna et al.[104] Rashid et al.[105] Viau et al.[106]
Postmenopausal hormone therapy	Chia et al.[96] Erdem et al.[107] Lin et al.[28] Schaumberg et al.[108]

* Accutane; Hoffman-LaRoche, Nutley, NJ; withdrawn from the market in 2009.

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Overlap of DED Symptoms and Clinical Signs of MGD

Study	Symptoms Assessed (all frequency)	Clinical Evaluations/ MGD Definition	% with Dry Eye Symptoms who also had MGD
Shihpai Eye Study (Lin, 2003)	Eye dryness Gritty/sandy Burning Sticky Watery/tearing Redness Lash crusting Eyes stuck shut (am)	Telangiectasis or gland plugging ≥ G1	61.7% (p = NR)
Bangkok Study (Lekhanont, 2006)*	Eye dryness Foreign body sensation Burning Discomfort Sticky Tearing	Telangiectasis, Collarettes, and Plugging	63.6% (p = 0.006)

Evaluation, Diagnosis and Grading of Severity of Meibomian Gland Dysfunction

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

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Testing Summary

- Symptoms (no validated survey)
- Expression (not widely accepted)
  - Quality/ Quantity
- Lid assessment
  - Redness (difficult to grade)
  - Irregularity
  - MG location
- Staining (fluorescein)
  - Photography
- Aq. Production (© 1903)

Stages of MGD

STAGE	CLINICAL DESCRIPTION	TREATMENT
STAGE 1	No *symptoms* of ocular discomfort, itching or photophobia *Clinical signs* of MGD based on gland expression Minimally altered secretions: Grade ≥2 - <4 Expressibility: 1 No ocular surface *staining*	*Inform* patient about MGD, the potential impact of diet and the effect of work/ home environments on tear evaporation, and the possible drying effect of certain systemic medications *Consider* eyelid hygiene including warming/ expression as described below (±)
STAGE 2	Minimal to mild *symptoms* of ocular discomfort, itching or photophobia Minimal to mild MGD *clinical signs* Scattered lid margin features Mildly altered secretions: Grade ≥4- <8 Expressibility: 1 None to limited ocular surface *staining* [DEWS grade 0-7; Oxford grade 0-3]	*Advise* patient on improving ambient humidity; optimizing workstations and increasing dietary omega-3 fatty acid intake (±) *Institute* eyelid hygiene with eyelid warming (a minimum of four minutes, once or twice daily) followed by moderate to firm massage and expression of MG secretions (+) *All the above, plus* (±) Artificial lubricants (for frequent use, non-preserved preferred) Topical emollient lubricant or liposomal spray Topical azithromycin Consider oral tetracycline derivatives
STAGE 3	Moderate *symptoms* of ocular discomfort, itching or photophobia with limitations of activities Moderate MGD *clinical signs* ↑ lid margin features: plugging, vascularity Moderately altered secretions: Grade ≥8- < 13 Expressibility: 2 Mild to moderate conjunctival and peripheral corneal *staining*, often inferior [DEWS grade 8-23; Oxford grade 4-10]	*All the above, plus* Oral tetracycline derivatives (+) Lubricant ointment at bedtime (±) Anti-inflammatory therapy for dry eye as indicated (±)
STAGE 4	Marked *symptoms* of ocular discomfort, itching or photophobia with definite limitations of activities Severe MGD *clinical signs* ↑ lid margin features: dropout, displacement Severely altered secretions: Grade ≥13 Expressibility: 3 Increased conjunctival and corneal *staining*, including central staining [DEWS grade 24-33; Oxford grade 11-15] ↑ Signs of inflammation: e.g. ≥ moderate conjunctival hyperemia, phlyctenules	*All the above, plus* Anti-inflammatory therapy for dry eye (+)

Key:

Meibum quality is assessed in each of 8 glands of the central third of the lower lid on a 0-3 scale for each gland: 0=clear meibum; 1=cloudy meibum; 2=cloudy with debris (granular); 3=thick, like toothpaste [range 0-24].

Expressibility of meibum is assessed from 5 glands: 0= all glands expressible; 1=3-4 glands expressible; 2= 1-2 glands expressible; 3=no glands expressible. This can be assessed in the lower or upper lid.

Numerical staining scores refer to a summed score of staining of the exposed cornea and conjunctiva. The Oxford scheme has a scale range of 0-15 and the DEWS scale has a scale range of 0-33.

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Stages of MGD

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Management and Therapy of Meibomian Gland Dysfunction

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

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Current Practice Patterns*

- Lid hygiene, warm compresses and lid massage
  - Cleaning of the lid margin with baby shampoo, cotton buds or wet towels, daily for 5-15 minutes
- Lubricants in cases with additional dry eye
- Topical antibiotic oint (moderate to severe)
- Systemic tetracyclines/ derivatives in recurrence
- Incision and curettage with optional steroid injection in chalazion

*Excerpted from Moorfields Manual, Wills Eye Manual (Guidelines for posterior blepharitis and meibomitis)

Current Practice Patterns

- World-wide variation
  - Underreporting → difficult to assess patterns
  - Underdiagnosis common, clinical follow-up irregular
- Lid warming and hygiene common
- Many use artificial lubricants
- Most Common Rx: Systemic tetracycline or derivatives (less frequent in EU/Japan)
  - 2nd most common Rx: topical antibiotic or antibiotic-steroid combination

Table 2. Clinical summary of MGD staging used to guide treatme

DISEASE STAGING			
Stage	**MGD grade**	**Symptoms**	**Corneal Staining**
1	+ (minimally altered expressibility and secretion quality)	Asymptomatic	None
2	++ (mildly altered expressibility and secretion quality)	Minimal to Mild	None to limited
3	+++ (moderately altered expressibility and secretion quality)	Moderate	Mild to moderate; mainly peripheral
4	++++ (severely altered expressibility and secretion quality)	Marked	Marked; central in addition
"PLUS DISEASE"	**Co-existing or accompanying disorders of the ocular surface and/ or eyelids**		

Recommended Staged Therapy

Stage =

1 **2** **3** **4** **Plus-**

+Disease Inform patient (about dietary / environmental / medication effects)
± Eyelid hygiene (warming / expression)

+Eyelid hygiene (warming / expression),
Advise re: potential benefits of ambient humidity / n-3 fatty acid,
~~± Lubricant/lipid, topical azithromycin, tetracycl. derivatives~~

+ Oral tetracyclines
± Ointment (pm), cyclosporine/steroid for DE

+ Anti-inflammatory therapy for DE

+ Steroids, CL, Surgery

Design and Conduct of Clinical Trials

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Reza Dana, M.D., M.Sc., M.P.H.
Michael A.Lemp, M.D.
Kelly K. Nichols, O.D., M.P.H., Ph.D.

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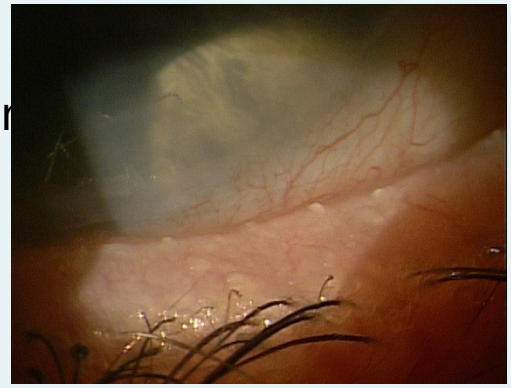
Existing Clinical Trials

Key Issues	Findings n = 26
Trial objective	Majority interventional treatment trials. 1/3 comparative (hot compresses or artificial tears).
Trial design /Methodology	Primarily small trials (<40 subjects) of short (<3 months) duration. Most prospective, 3 randomized controlled design, & 2 were double masked.
Study population	Chronic disease but selection criteria not uniformly defined; lid changes & symptoms most common clinical characteristics.
Inclusion criteria	No specific and consistent criteria; most common are lid margin signs (80%), dry eye findings (50%), symptoms of discomfort/foreign body sensation
Exclusion criteria	Classification of exclusion criteria in three different categories: 1) Ocular disease related/CL wear (most common); 2) Iatrogenic (e.g surgery, 1/3 studies); 3) Systemic disease related/pregnancy (15%).

Existing Clinical Trials

Issue	Findings n = 26
Outcome measures	1. Symptoms 2. TBUT 3. MG secretion/expressio 4. Schirmer 5. Corneal staining 6. MG obstruction 7. Eyelids 8. Lipid layer
Treatment	Most lacked washout period & did not check for relapse; 50% allowed concurrent use of other treatment & 30% treatment in the control group; large variability between Tx duration but pharmacological trials tended to be longer with follow up.
Statistics	Limited number of RCTs available; difficult to calculate effect size, power or required sample size. Limited information on how missing data e.g. loss to follow up, exclusion due to non-compliance, were handled.



Summary

Priorities for future clinical trials:

- Additional randomized, controlled, double-masked treatment trials with clearly defined objectives, relevant outcome measures based on pathophysiology, and refined inclusion & exclusion criteria
- Determination of the natural history of MGD
- Further understanding of the association with dry eye disease (and risk factors)
- Development and validation of a symptom questionnaire specific to MGD.

A Report from the TFOS International Workshop on Meibomian Gland Dysfunction

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Thank You!

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