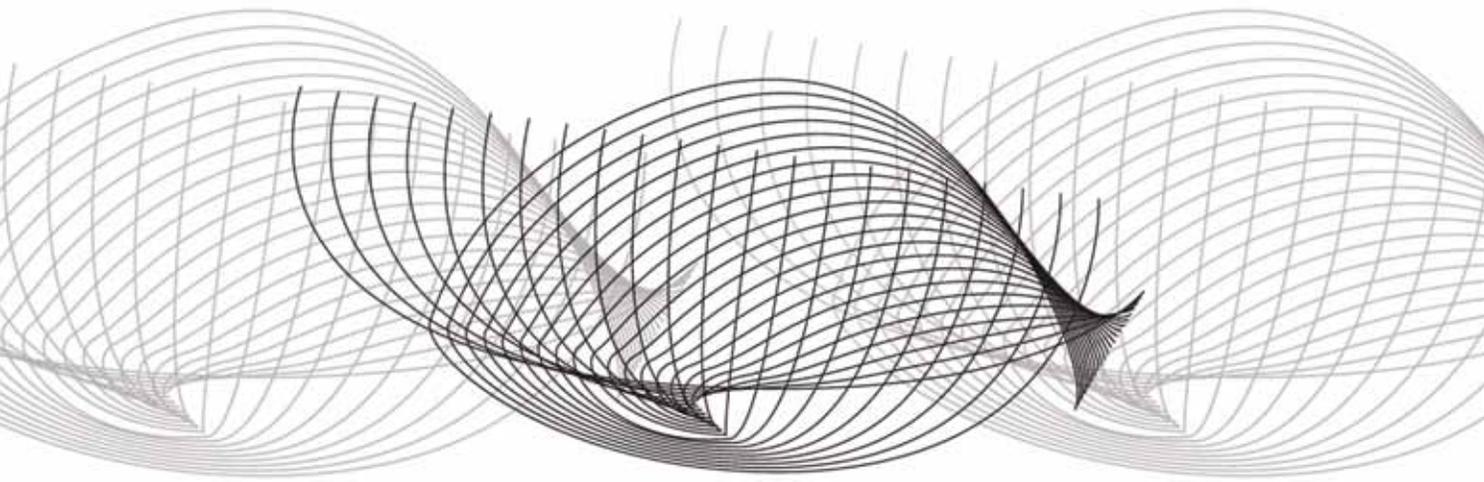


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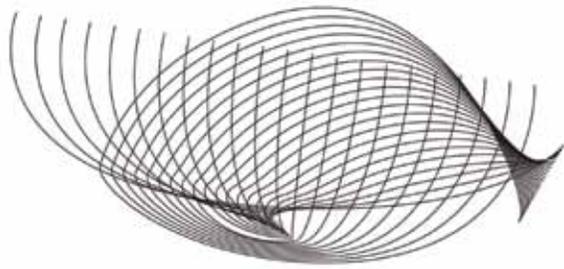
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# **Meibomian gland dysfunction**

From theory to daily ophthalmic practice



# Introduction

The term 'Meibomian Gland Dysfunction' (MGD) was first used by Korb and Henriquez in 1980,<sup>1</sup> and has given impetus to the study of the disease. According to some reports, up to 70% of people<sup>2</sup> suffer from MGD. Given the prevalence of the condition, which is the major cause of evaporative dry eye and possibly of dry eye overall,<sup>3,4</sup> MGD therefore represents an important disorder in need of management.

The assessment, diagnosis and management of the condition have been inconsistent in the past, due to the lack of a clear definition and classification of MGD. To combat this, the Tear Film and Ocular Surface Society (TFOS; [www.TearFilm.org](http://www.TearFilm.org)) convened the International Workshop on Meibomian Gland Dysfunction, involving an international group of clinicians and research scientists who reviewed the causes, pathophysiology, diagnosis and treatment of the condition. Over a two year period, and with sponsorship from several pharmaceutical companies, including Laboratoires Théa, the Workshop has now produced a definitive, evidence-based assessment of MGD, which can be regarded as a milestone event.

At the 2011 EVER Congress in Crete, Greece, Laboratoires Théa held a symposium to present some of the information from the workshop as well as ways to put the treatment recommendations into daily ophthalmic practice. In this supplement we will present some of the highlights of this symposium.

## A collaborative approach

TFOS is a non-profit organization dedicated to advancing the research, literacy and educational aspects of the scientific field of the tear film and ocular surface throughout the world. As part of this work, TFOS sponsors the International Workshop on Meibomian Gland Dysfunction, a collaborative project researching the subject of MGD.

"Of course, industry support was important for the success of the workshop and Théa has played a prominent role. **Recently, Théa supported the dissemination of the conclusions of the workshop across Europe and arranged translations into 10 different languages (French, German, Italian, Spanish, Portuguese, Dutch, Polish, Turkish, Russian and Greek) helping everyone to understand the disease better,**" according to Professor Anthony Bron.

"The workshop's intention," he continued, "was to conduct an evidence-based evaluation of meibomian gland structure, function and dysfunction, devise a contemporary definition and classification of MGD, assess methods of diagnosis and grading, appraise clinical trial design, review the literature and make recommendations for management and therapy." The final reports of the International Workshop<sup>4-12</sup> were published earlier this year in *Investigative Ophthalmology & Visual Sciences (IOVS)*. The separate parts of this TFOS MGD report have immediately become the most requested papers in the all time best list of *IOVS*, which indicates the utmost importance of MGD and the respective very high interest of the ophthalmological community.

### With contributions from

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**Figure 1:** Stagnated meibomian secretions. Courtesy of Prof. Benitez Del Castillo.



# MGD report highlights: Theory

Professor Erich Knop re-stated the definition of MGD developed at the workshop:

## Definition

***“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. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.”<sup>5</sup>***

“That is the first definition of MGD and derived through global consensus,” explained Prof. Erich Knop. “To go a bit more into detail, when MGD is stated to be diffuse, it means it does not affect all of the roughly 30 single meibomian glands that we have along each lid margin, but usually only some of them at varying numbers and degrees.”

**“Obstruction of the terminal duct and orifice due to hyperkeratinization is one of the important factors: the secretum (meibum) cannot get out and is stuck inside the gland. Another contributing factor is qualitative and/or quantitative changes in the glandular secretions. Both of these — the hyperkeratinization and the qualitative change in secretion — result in obstruction,”** he added.

## Classification

“Terminologically, as originally defined by Foulks and Bron in 2003,<sup>13</sup> one important step in the classification is to differentiate between disease and dysfunction,” said Prof. Knop. ‘Meibomian gland disease’ is, in this respect, the correct term to use for a broad range of disorders, including congenital, neoplastic or acute conditions, among others. “However,” he added, “the dysfunction, specifically refers to a chronic, usually obstructive, condition of the Meibomian glands. We have to differentiate between low and high delivery states, of which the low delivery states are most prevalent.”

The division of MGD into low and high delivery states has further sub-classifications. The low delivery state has two forms: hyposecretory and obstructive. The MGD resulting from systemic retinoid toxicity would be an example of a hyposecretory state. More often, obstructive MGD is encountered and this may exist in cicatricial and non-cicatricial forms. The cicatricial form occurs, in particular, in the presence of cicatricial conjunctival disease such as Stevens Johnson syndrome and trachoma but cicatricial and non-cicatricial changes may also occur together in the same

***“You can imagine that such a complicated gland structure gives rise to a lot of pathological insults, which is in fact the case in MGD.”***

*Professor Erich Knop*

lids, in the absence of tarsal conjunctival scarring. There is also a ‘hypersecretory’ or ‘high delivery’ state in which light pressure on the eyelid over the glands expresses copious meibum discharge. **MGD most frequently occurs in the low delivery form, and is most often caused by obstructive disease (more specifically, by obstructive non-cicatricial disease).**

## Anatomy, physiology, pathophysiology and epidemiology

Understanding the anatomy of the meibomian gland is key to understanding MGD. The glands themselves are single, large and sebaceous but are not directly associated with hair follicles. They are located in and almost completely fill, the lower and upper tarsal plates of the eyelids.

Meibomian glands contain several acini, where the secretion of the meibomian oils (meibum) is performed by the secretory cells (meibocytes). These acini are connected by lateral ductules to a main, long, straight duct, which runs through the centre of the gland. The meibum is then delivered through an excretory duct onto the posterior part of the lid margin. “You can imagine

***“If you diagnose MGD too late or treat it too late, then the gland may already be burnt out and so you’ve lost your therapeutic options.”***

*Professor Erich Knop*

that such a complicated gland structure gives rise to a lot of potential pathological insults, which is in fact the case in MGD,” explained Prof. Erich Knop who is the chair of the MGD Workshop Subcommittee for Anatomy, Physiology and Pathophysiology of the meibomian glands.

Physiologically, it is necessary to differentiate between the actual secretion of oils, which takes place in the acini (mostly a long distance from the posterior lid margin surface), and their delivery. The delivery is out of the gland, through the excretory duct, onto the lid margin. The secretion results from the constant division and maturing of cells that eventually disintegrate to form the meibomian oils, but the delivery needs some help, which is given by the contractile forces of the orbicularis and the muscle of Riolan during the blink. That these muscles play a role is indicated by the fact, that blinking has a significant impact on the delivery of meibum. A lack of blinking leads to a deficiency of oil delivery onto the lid margin and, in reverse, intentional forceful blinking leads to increased oil on the lid margin and in the tear film lipid layer and hence represents a therapeutic option in incipient MGD, noted Prof. Knop.

Hormones are a major driving force for the meibomian glands: androgens are generally a positive stimulus for the differentiation and function of the ocular surface tissues and glands, whereas estrogens are negative for gland function.

This could be relevant to the greater prevalence of MGD in women as well as a general increase of MGD with advancing age. Apart from this, ethnic factors are to be considered since Asian populations generally have a distinctly increased rate of

MGD. The prevalence and incidence of MGD is also influenced by several systemic and ocular diseases and are affected by respective systemic and topical medications, as well as potentially by diet.

**Describing the pathology of MGD, Prof. Knop explained that the gland orifices are obstructed by plugs of thickened, opaque, whitish secretion containing keratinised material, as already observed by Korb and Henriquez in 1980, which reduces the delivery of meibum onto the lid margin. This results, in a direct deficiency of oil in the tear film lipid layer and hence to the onset of evaporative dry eye.** In a gland that has become obstructed because of hyperkeratinization and/or thickened secretum, the glands become more prominent as whitish streaks that are clinically visible through the everted conjunctiva. **The orifices are prominent by the obstructing material as whitish spots on the posterior lid margin.** Consequently, there is a resultant build up of pressure inside the glands that causes a ductal dilatation and a pressure atrophy of the acini, which degenerate and can no longer produce oils. Eventually, this can lead to a section or the complete gland epithelium becoming keratinized.

*“If you diagnose MGD too late or treat it too late, then the gland may already be burnt out and so you’ve lost your therapeutic options,”* asserted Prof. Knop.

### Current practices assessed

“The goal of the Management subcommittee, which I was proud to chair, was to review current practice. We assessed the published scientific literature comprehensively, identified areas of conflict or of deficient evidence and noted concepts requiring further research. A crucial aim was to grade the level of published evidence according to an accepted scale,” said Professor Gerd Geerling.

***“...eyelid warming and mechanical hygiene, is widely considered to be effective for MGD.”***  
*Professor Gerd Geerling*

The subcommittee found that current practice included the application of eyelid hygiene, warm compresses and lid massage and the use of artificial lubricants and systemic tetracyclines (more common in the US). However, there was no consensus between various institutions and textbooks regarding the details of the recommended treatments (i.e., how long heat should be applied, the duration and location of eyelid massage, etc.), in fact, huge variation exists.

“When we were discussing these options, then, not at a textbook level but on the level of the attending colleagues and experts in the field, we again found worldwide variation,” Prof. Geerling explained.

Additionally, the subcommittee found it difficult to assess patterns because of under-reporting of the conditions. Under-diagnosis was also commonplace and clinical follow-up was found to be irregular.

Over 140 papers were reviewed in total and a list of identified treatment modalities was created (Table 1). Of these treatment

modalities, many were insufficiently rigorous, according to the grading scale, and each had associated advantages and disadvantages. **“However, eyelid warming and mechanical hygiene,”** added Prof. Geerling, **“is widely considered to be effective for MGD, despite the lack of standard techniques and uncertainty of compliance.”**

Prof. Geerling explained that it was imperative to develop a staging approach to MGD, to recommend appropriate treatments.

The Management subcommittee therefore compiled its own disease staging schema. This has four stages ranging from asymptomatic to severe disease, which can be modified by a ‘plus disease’ grade that is characterized by the presence of co-existing or accompanying disorders of the ocular surface and/or eyelids. Recommended treatment modalities for the disease staging as set out above can be found in Table 2.

“In the future,” said Prof. Geerling, “more research will be needed in those areas where evidence is lacking. This is essential if industry is to target MGD appropriately and develop new pharmacological treatments. The current focus on MGD should provide a good prospect for further development in this area.”

**Table 1: The treatment modalities identified by the literature review.<sup>11</sup>**

• artificial lubricants*
• topical lipid supplements
• mechanical lid hygiene and warm compress or heat application
• topical antibiotic agents
• treatment of demodex infestation
• use of tea tree oil
• systemic antibiotics
• essential fatty acids
• steroid therapy, including intralesional steroids for chalazae
• calcineurin inhibitors
• sex hormones
• surgical treatments
(*There were no specific instances of artificial lubricants being prescribed for MGD, only for associated conditions, including blepharitis and aqueous-deficient dry eye)

**Table 2: Recommended treatment modalities for MGD based on the Management subcommittee’s disease staging**

DISEASE STAGE	RECOMMENDED TREATMENT
1	Inform patient about dietary and environmental options, potential side effects of other medications and that eyelid hygiene may overcome this
2	Eyelid hygiene, plus (potentially) lubricants (for frequent use, non-preserved preferred) and/or systemic medication
3	As above, plus oral systemic tetracyclines, frequent and regularly; potentially augmented with topical steroids
4	As above, plus topical steroids or other anti-inflammatory medication
“Plus” disease	As above, plus treatments specific to each disease

# Managing MGD: Implementing TFOS recommendations into daily practice

A great variety of options for treating MGD exist, with varying degrees of evidence supporting each option's use.

**However, eyelid hygiene is regarded as the mainstay treatment of MGD. This usually involves the application of warm compresses or heat to the lids combined with mechanical massage.** To understand how this became the mainstay treatment it is important to first consider the history of MGD management.

## History of MGD management

**"We now know that MGD is the most common cause of dry eye,"** suggested Professor Zbigniew Zagórski. "However, some decades ago it was different. Twenty-five years ago we first discussed the role of meibomian glands: it seemed to us very basic and not very relevant to everyday practice, but over time, we have become convinced that this really is an important problem."

According to Prof. Zagórski, many of the recent findings of the MGD Workshop were already known to a handful of researchers. However, before the awareness of MGD was widespread, many patients with this form of posterior blepharitis were treated for conjunctivitis, allergies and so on, and no lid hygiene measures were encouraged in these patients.

**"Now we recognize it as a chronic disease requiring long-term management, and one of the most common reasons for iatrogenic damage to the ocular surface,"** said Prof. Zagórski.

(Figure 2)

## Evaluation of patients

Prof. Zagórski described his experience in attempting to adopt the recommendations of the Workshop in Poland, adapting its findings in response to the constraints imposed by insufficient resources. To aid this, conscious of the importance of quantifying the symptoms of MGD, Prof. Zagórski and colleagues translated the Ocular Surface Disease Index (OSDI) into Polish to use in daily practice. After implementing various aspects of the Workshop's recommendations, proper treatments could be provided and improvements in management were quickly seen.

Further to this work and as a result of recent interest in Marx's line, Prof. Zagórski is assessing correlations between the status of this line and MGD in the hope that it may help in patient evaluation.

## Demodex

The role of Demodex has recently been raised again. This is a controversial area because Demodex is a very common skin parasite. However, there is evidence that Demodex infestation contributes to anterior blepharitis and it may be that it aggravates MGD when anterior blepharitis and MGD are combined, which is not uncommon.

Formerly, treatment methods were confined to cleaning the lid with alcohol and some ointments, which was not very efficient. Now tea tree oil has been recommended by Tseng to combat anterior blepharitis caused by Demodex, although the effect of killing these mites on any concomitant MGD has not been determined.<sup>11</sup>

## Preoperative evaluation

"We are also," said Prof. Zagórski, "now starting to address asymptomatic disease, detected by Meibomian gland expression, at least by informing patients about the value of lid hygiene. Before cataract surgery, I believe we should be more aggressive in treating

asymptomatic MGD." He reported that **post-cataract surgery asymptomatic MGD frequently becomes symptomatic.**

**"It is not easy to convince patients to have treatment if they are asymptomatic, however, we can assert that, as is the case in glaucoma, it can start as a very mild form and may progress to a more severe form, which is more difficult to control,"** added Prof. Zagórski.

## Treatment options

In patients where eyelid hygiene is not effectively relieving the obstructive form of MGD Prof. Zagórski recommends meibomian gland probing according to Maskin. He noted that this technique may be useful in patients complaining of heavy, gummy lids and lid tenderness but it should not be used in cases of cicatricial MGD. However, at present, the most commonly recommended treatment option remains eyelid hygiene therapy.

[Implemented, when necessary, with measures recommended by the *International Workshop of MGD*]

## Eyelid hygiene

The physiological melting point of meibum is around 32 °C, but in MGD patients this melting point increases to a minimum of 35 °C.<sup>13</sup>

**The aim of eyelid hygiene therapy is to melt the meibum, to allow it to be expressed and to prevent obstruction of the terminal ducts.**

As shown in Table 2, eyelid hygiene is recommended for every stage of MGD and so it is critical to communicate its benefits to patients.

"The first message is to apply heat and massage 'once or twice daily'. This is my recommendation," commented Dr Serge Doan.

**"Every day — even if the patient is symptomatically OK, he should perform this lid hygiene on a regular basis, because MGD is a chronic disease."**

The three steps crucial to proper lid hygiene are eyelid warming, eyelid massage and eyelid cleansing.

- With **eyelid warming**, the temperature should be monitored, because the aim is not to burn the eyes but to melt the meibum within the glands, explained Dr Doan. **"But I think the duration is more important than the temperature; not too hot, but for long enough — at least four to five minutes."**
- **Eyelid massage** must be performed at the correct location (at the level of the meibomian glands) and the patient must employ the correct technique: pressing the eyelids to the eyelid aperture, or from the nose to the ear, or pinching the lids. The massage should last for between 30 seconds and one minute; any longer and it may irritate the lids.
- **Eyelid cleansing** is especially important if the patient has associated blepharitis, for instance with crusts at the level of the eyelid margin; specialist ophthalmic cleansing products are available to deal with this task.

# A new eyelid warming device: Blephasteam

Although lid hygiene is a popular and effective treatment for MGD, it is a complex process, and its efficacy can be reduced by lack of patient compliance and lack of clear direction from the physician about implementation.

**“In fact the main problem with eyelid hygiene is compliance, and if the patient does not understand what to do, how to do and when to do it, he will not do it,” explained Dr Doan, who clarified that: “Inadequate eyelid warming duration is one of the main aspects of non-compliance.”**

In response to these compliance concerns, Laboratoires Théa has developed the therapeutic medical device Blephasteam ([www.blephasteam.com](http://www.blephasteam.com)).

## What is Blephasteam?

The Blephasteam eyelid warming device (Figure 3)<sup>14,15</sup> incorporates a heating device, with a chamber that will heat up to 42 °C (Figure 4),<sup>15</sup> a temperature high enough to melt meibomian secretions and obstructions without harming the lid skin.<sup>15</sup> In a separate chamber, the device also includes a sponge, which, when moistened with mineral water, will generate humidity in the chamber.

**“So you have a warm chamber at 42 °C and also a wet chamber, which is very useful, of course, in dry eye patients.** The device is plugged into the A/C for a preliminary period and the application lasts 10 minutes,” explained Dr Doan.

## Efficacy

A recent study<sup>16</sup> compared the new Blephasteam device with traditional hot compresses. A major feature promising superior efficacy of Blephasteam, is that, unlike the situation with a compress, the device has a stable temperature over the full period of application.

In an interventional prospective uncontrolled study<sup>17</sup> of MGD patients conducted over 21 days in three French centres, Dr Doan concluded that the Blephasteam eyelid warming device is a promising alternative to classical lid hygiene techniques, although the technique is not suitable for every patient.

“Signs and symptoms of MGD decreased significantly. What was surprising about this study was that there was no effect on break-up time, and also no effect, at least statistically, on tear osmolarity, but maybe we should have included more patients,” commented Dr Doan.

The study did show, however, that the device is safe to use, and ocular pressure was stable in all patients, even immediately after the treatment.

## Assessing the usefulness

**“Overall, patient satisfaction after using Blephasteam was very good,” noted Dr Doan. “The patients reported that the device was really comfortable for them.”**

Efficacy results have also been encouraging,<sup>13–19</sup> perhaps reflecting the stability of the Blephasteam temperature compared to that of the hot compress.

“A particular problem with traditional compresses, for instance applying a face cloth for the correct period of time,” Dr Doan pointed out, “is that activity is completely limited during treatment. This can be very difficult, especially when dealing with children. But there are clear windows in the Blephasteam device, so that, during a Blephasteam treatment session, people are able to work on the computer, to read, to watch TV or to play on their Nintendo console. Patients may keep their eyes open and blink freely, which allows for better meibum excretion. Despite the humidity inside the chambers, the device does not mist up during use.”<sup>15</sup>

**Figure 2:** Severe irreversible anterior segment iatrogenic damage due to misdiagnosed and mistreated blepharitis and dry eye. The treatment included topical anaesthetics, steroids, NSAIDs, antibiotics, immunosuppressives etc.



**Figure 4:** A representation of the Blephasteam device demonstrating how the chambers deliver heat and moisture to the eyes.<sup>15</sup>



**Figure 3:** Blephasteam eyelid warming device, in use by patients of varying ages and demonstrating ability to keep eyes open during eyelid warming.



# Conclusions

MGD is a common and important condition that influences the health and well-being of millions of people. Its prevalence is probably underestimated and recent reports suggest that it may be the most frequent cause of dry eye disease.

There is much more to be learnt about its mechanism and fresh approaches to diagnosis and treatment may offer new opportunities in the future. Currently, many treatment options exist though they are of varying efficacy. The TFOS International Workshop provided a definitive assessment of the disorder, including its pathophysiology, diagnostic methods and a review of historical and current treatments. The workshop highlighted where evidence is lacking and where more research is needed.

The aim of Laboratoires Théa has been to disseminate the conclusions of the report to the greatest number of

specialists around Europe in order to increase their knowledge and awareness of this common pathology. Their new MGD device, Blephasteam, has been developed on the basis of the most recent understanding of MGD. While it has some disadvantages, it nevertheless represents a convenient and safe treatment option for most MGD patients.

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## Case studies: tips and tricks

Presented by Pierre-Jean Pisella.

**A** key feature of aqueous phase dry eye and a number of ocular surface diseases, is the inflammatory reaction at the ocular surface, which may have several aetiologies.

In a previous study we found that the inflammatory population was increasing in patients with kerato-conjunctivitis sicca with inflammatory markers, as well as in patients with MGD. At the same time we also studied the mucin concentrations in goblet cells. It was dramatically decreasing in both situations.

This emphasizes that although we may have two different pathologies, we can still have the same clinical features in the conjunctiva. The clinical point is to analyse both eyelids of the patient, and that's exactly what the Workshop in 2007 said, that MGD is part of the 'vicious circle' of inflammation encountered in dry eye, although it must be stated that in the TFOS MGD Report, it was clearly characterized as a typically non-inflammatory disorder.

I want to share with you a case that brings out this point.

### Clinical cases

A 72-year old French man was diagnosed at his first consultation with severe dry eye syndrome, with a moderate reduction of visual acuity in one eye. There was corneal involvement and the patient was treated with artificial tear substitutes; we examined the eyelids and found blepharitis associated with meibomian gland dysfunction.

We continued the treatment, along with eyelid hygiene. Three months later we had achieved stability of visual acuity but not much improvement in functional symptoms such as eye burning and itching.

What can we do for this kind of patient? He was instructed to perform eyelid hygiene and he carried out his massage well. But should we add

topical antibiotic or anti-inflammatory therapy?

After a short period of using steroids, I decided to introduce immunosuppressor twice a day into his regime. With this, while continuing the eyelid hygiene and artificial tears, we obtained stability for the patient.

There is not much literature about the use of immunosuppressor in MGD or of steroids in similar cases, but it would be useful to keep both in mind. I think that the efficacy of immunosuppressor in this patient was due to its general action as an anti-inflammatory agent, without any specificity.

In a further case, another old man was referred by his ophthalmologist, who explained that she wanted me to investigate his eyes and maybe to do a conjunctival biopsy, to see if there was some very severe problem.

When I received his medical history, I saw he had been treated for open angle glaucoma for 10 years with preserved betablockers, without any problems. However, he'd recently changed his treatment because of a rise in intraocular pressure. The patient felt a difference and became symptomatic: This wasn't due to MGD, but what was the pathology?

The ophthalmologist decided to stop the new medication for 15 days without any result, and she then used topical steroids. For a week the eyes improved, but then they became worse and so I stopped all treatment for one month. This was successful in relieving symptoms and the inflammatory changes at the ocular surface. It appears that this was an allergic reaction, which was a surprising finding in this patient. If you suspect this may be the case with one of your patients, always see them at least one month after cessation of treatment, as a therapeutic check.

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