The ocular surface 2022; Volume 26, pp. 211-221 (DOI: 10.1016/j.jtos.2022.08.010)

Antibiotic Treatment for Dry Eye Disease Related to Meibomian Gland Dysfunction and Blepharitis – A Review

Ragnheidur R. Vernhardsdottir[1], Morten S. Magno[2-6], Leif Hynnekleiv[2,7], Neil Lagali[6,8], Darlene A. Dartt[9], Jelle Vehof[1,3,7,10,11], Catherine J. Jackson[4], Tor P. Utheim[1,2,4,12]

[1] Department of Ophthalmology, Vestfold Hospital Trust, Tønsberg, Norway
[2] Department of Plastic and Reconstructive Surgery, Oslo University Hospital, Oslo, Norway
[3] Department of Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[4] Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway
[5] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[6] Department of Ophthalmology, Sørlandet Hospital Arendal, Arendal, Norway
[7] Department of Twin Research & Genetic Epidemiology, King's College London, St Thomas' Hospital, London, United Kingdom
[8] Division of Ophthalmology, Department of Biomedical and Clinical Sciences, Faculty of Medicine, Linköping University, Linköping, Sweden
[9] Schepens Eye Research Institute/Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, 20 Staniford St., Boston, MA 02114, United States
[10] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[11] Dutch Dry Eye Clinic, Emmastraat 21, 6881SN, Velp, The Netherlands
[12] The Norwegian Dry Eye Clinic, Oslo, Norway

Abstract

Background: Dry eye disease (DED) is among the most prevalent ophthalmic conditions but is often underdiagnosed and mistreated. Antibiotics are regularly used to treat DED caused by meibomian gland dysfunction (MGD) or blepharitis, but their use has been questioned.

Objective: To critically evaluate the use of oral and topical antibiotics in DED management.

Methods: A literature search was conducted on November 15th 2021, in the PubMed database. The search terms were: *(antibiotics OR azithromycin OR doxycycline OR minocycline) AND (dry eye disease OR meibomian gland OR blepharitis anterior OR blepharitis posterior OR chronic blepharitis)*. All relevant original articles with English full-text were included. Case reports and review articles were excluded.

Results: The search provided 619 articles, of which 22 met the inclusion criteria. Oral and topical antibiotics appeared to have short-term positive effects on signs and symptoms of blepharitis- or MGD-related DED. However, these improvements often reverted upon cessation of treatment. The need for repeated treatments and mild adverse events were common.

Conclusions: Current evidence suggests that patients with blepharitis- or MGD-related DED experience short-term benefits of antibiotics. However, evidence for lasting improvement after completed treatment was lacking. Given the unclear long-term benefits, common side effects, and increasing antibiotic resistance seen globally, the existing literature is not sufficient to conclude that antibiotics are useful in long-term MGD management. A survival-analysis of a single round of antibiotics, in addition to the effects of repeated rounds of treatment, on DED parameters could provide useful insights.

1 Introduction

Patients with dry eye disease (DED) typically experience fluctuating-to-constant ocular irritation, pain, photophobia, and blurred vision. Although DED is highly prevalent, it is considered the most underdiagnosed and mistreated condition in ophthalmology (1). DED affects between 5% to 50% of the population, depending on the definition used and population studied (2). Age (2, 3), female sex (2-4), and screen use (2, 3, 5) are among the most important risk factors for DED. The prevalence of DED is expected to grow, with the rising average age of the population (6), and increased reliance on screen use (2), which was accelerated by the Covid-19 pandemic (7). DED symptoms vary from mild to debilitating and have a significant impact on quality of life (2, 8). The economic costs of DED from decreased productivity and increased absence from work in the US alone are estimated to be roughly 55 billion U.S dollars annually (9).

Once established, DED can become a self-sustaining vicious cycle, as shown in **Figure 1**. The prescription of antibiotics is common for moderate-to-severe DED (10), especially when associated with meibomian gland dysfunction (MGD) and blepharitis (11). Antibiotics are one of the biggest breakthroughs of modern medicine. However, the World Health Organization advises limiting the prescription of antibiotics to slow the development of antibiotic resistance (12). Recent reviews have found that oral and topical antibiotics are effective in treating MGD and MGD-related DED, especially in the short-term (13-17). However, despite their widespread use, level I clinical evidence (randomized, placebo-controlled trials) supporting the use of oral antibiotics in the treatment of MGD and MGD-related DED is limited (13, 14, 16). Therefore, it remains necessary to evaluate whether the

potential gains available from this treatment modality outweigh the potential risk from an individual and public health perspective.

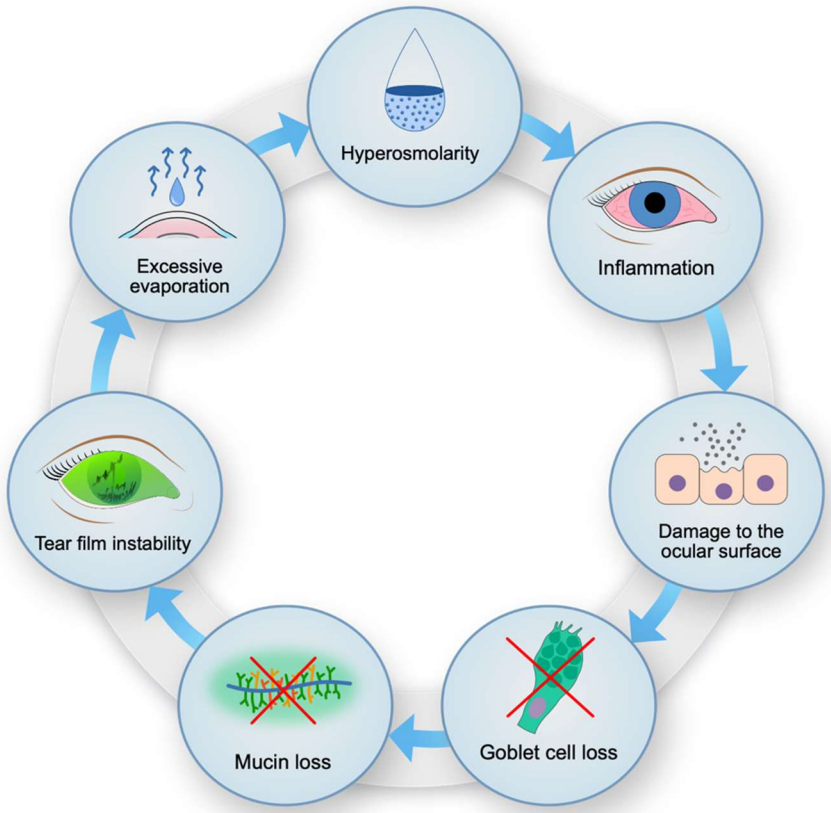
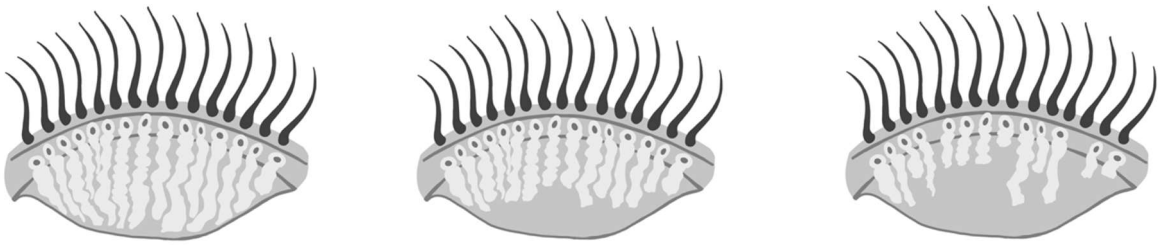


Figure 1. The vicious cycle of dry eye disease. Once initiated, the vicious cycle of dry eye disease can be perpetuated by several interconnected steps that collectively promote dry eye development and may be hard to break. Figure credit: Sara Nøland.

MGD is a common cause of loss of tear film homeostasis, resulting in evaporative dry eye (18). Reduced meibum quality and quantity destabilizes the tear film and leads to increased evaporation and tear osmolarity (18, 19). Meibum thickening and terminal duct obstruction is often found, causing meibum stasis, cystic dilation, acinar atrophy, and gland dropout (**Figure 3**) (20-22). Intraductal meibomian gland probing has in recent years been used for patients with refractory obstructive MGD, sometimes in combination with local antibiotics (23). MGD is sometimes accompanied by local inflammation and bacterial proliferation in the meibomian gland and eyelash area, a condition known as blepharitis

(24). Blepharitis is a common disease of the eyelids, characterized by redness, itching, and greasy and crusty eyelashes (25). It is divided into anterior blepharitis, affecting the anterior lamella of the eyelids, and posterior blepharitis, caused by MGD and affecting the posterior lamella (25). Blepharitis is generally chronic in nature and is frequently associated with other conditions like chalazion, acne rosacea, and DED (26).



(a) (b) (c)

Figure 2. Illustrations of meibography, showing (a) healthy meibomian glands, (b) meibomian gland dysfunction with moderate glandular atrophy, and (c) severe meibomian gland dysfunction with atrophic glands and gland dropout. Figure credit: Emily Moschowits.

The density of microbiota of the ocular surface in a healthy eye is extremely low and the types of microbes are restricted, especially compared to that of other areas of the body (27). This is partly due to mechanical wiping during blinking, sloughing of epithelial cells, and antimicrobial proteins in tears. Secretory IgA, which prevents adhesion of microbes to the epithelia and enhances phagocytosis by neutrophils; lysozyme, which is directly toxic to bacteria; and lactoferrin, which reduces available nutrients for microbial growth, are naturally found in tears (27). Together, these factors inhibit microbial infection of the ocular surface. Despite this, a healthy commensal ocular microbiome appears to be important and contributes to local immune activation and defense against infections (28-30). Destabilization of the tear film and disruption of ocular surface homeostasis diminishes defense against microbial invasion (27).

Furthermore, the lid margins of those with blepharitis contain more commensal bacterial species than unaffected individuals (19). It is, however, unclear if this bacterial colonization, experienced by patients with MGD and blepharitis, reflects infection as a driver of disease development, or merely an increased susceptibility to bacterial colonization (1). Bacterial colonization promotes the production of toxic compounds and pro-inflammatory molecules, such as lipases and matrix metalloproteinases (MMPs) (14).

Local or systemic antibiotics, including doxycycline, minocycline, or azithromycin, are regularly used to manage MGD (11, 13) and blepharitis (31) due to both their antimicrobial and their anti-inflammatory properties (**Figure 4**) (11, 13). Antibiotic use aims to break the vicious cycle of impaired meibum consistency, bacterial infection and toxin production, inflammation, and tear film instability seen in MGD (**Figure 4**) (32) and blepharitis (26).

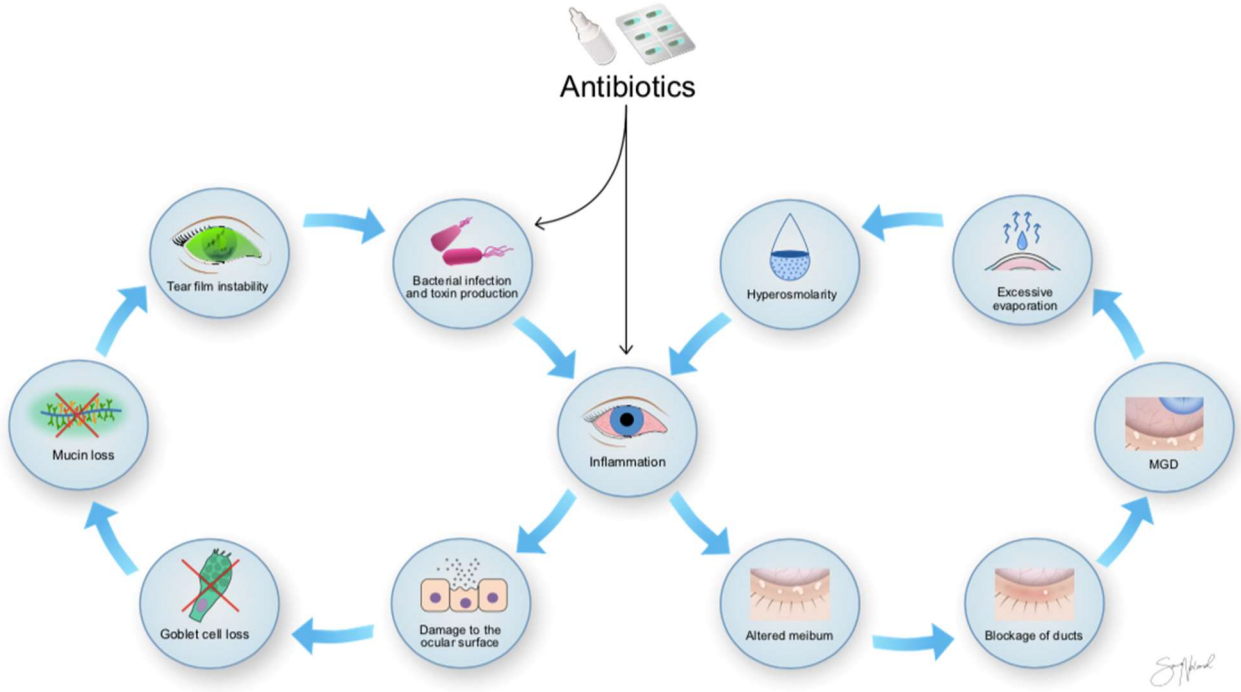


Figure 3. The vicious cycle of meibomian gland dysfunction-related dry eye disease and target points of antibiotics. Antibiotics could potentially break the vicious cycle through two mechanisms: eradication of bacteria and reducing inflammation, as illustrated in the figure. Figure credit: Sara Nøland.

Tetracyclines are a class of antibiotics that were first used in the treatment of blepharitis in 1951 as topical drops and ointments (33). Their anti-inflammatory and anti-metalloprotease properties were discovered later, and their use in inflammatory diseases started in the 1980s (34). Treatment with tetracycline agents, and other anti-inflammatory antibiotics, is recommended by international guidelines for treating moderate-to-severe cases of MGD-associated DED (10, 11).

Doxycycline is a long-acting tetracycline antibiotic that is often prescribed for both blepharitis (31) and MGD management, due to fewer side effects, a higher tissue concentration and a longer half-life than classic tetracycline (11, 35, 36). However, the effectiveness of tetracycline antibiotics has been challenged by increased microbial resistance (37).

More recently, azithromycin, a broad-spectrum macrolide antibiotic with robust antimicrobial and anti-inflammatory properties (38), has been found to outperform doxycycline in DED treatment (39, 40). Azithromycin can reduce eyelid and ocular surface inflammation and aid in MGD management (10, 41).

Despite the widespread use, antibiotic treatment of DED related to MGD or blepharitis has come under scrutiny due to lack of clinical evidence for this indication (13, 42). In addition, side-effects are common. Oral tetracyclines often cause gastrointestinal (GI) distress, including abdominal discomfort, nausea, vomiting, and anorexia (43). Common side-effects of systemic macrolides are GI symptoms, such as diarrhea, abdominal pain, nausea, and vomiting (44). Severe and even life-threatening side-effects have been reported from both classes of antibiotics (43, 44). An overview of reported side-effects of oral tetracyclines and macrolides can be seen in **Figure 5**.

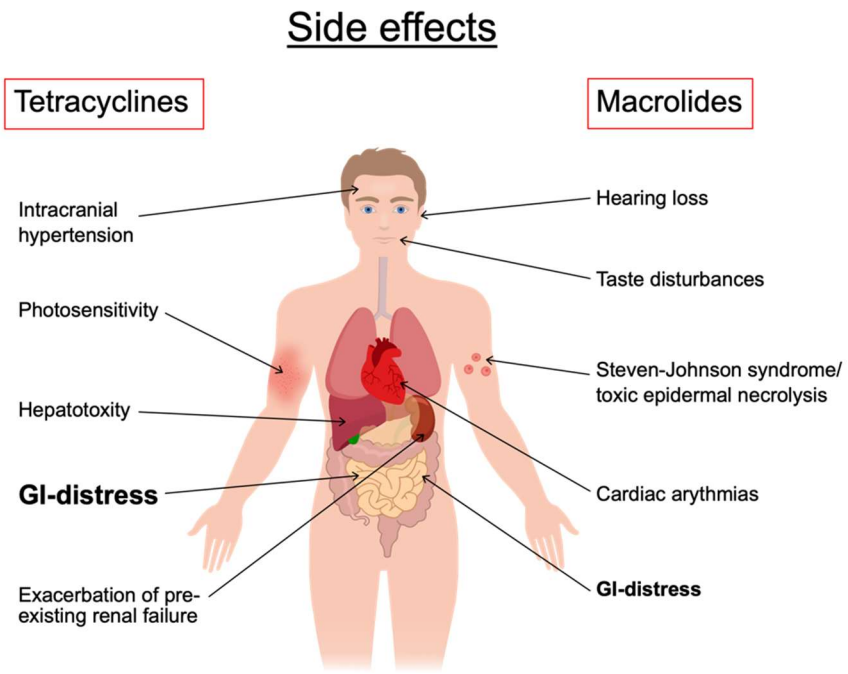


Figure 4. Reported side-effects of oral tetracyclines (doxycycline and minocycline) and macrolides (azithromycin). GI-symptoms are the most frequently reported side-effect of both medications/treatments. Figure credit: Sara Nøland.

Repeated oral antibiotic use, which is often practiced in patients with DED (39), negatively affects the microbiome in all parts of the body, including the ocular surface, gut, and skin, potentially leading to further complications. Typical antibiotic treatment with systemic tetracyclines lasts for one to three months and repeat treatment is often recommended (10, 11, 45). These several courses of treatment represents a considerable exposure to antibiotics, that could, in addition to the effect on each individual, also contribute to the global evolution of antibiotic resistant bacteria (12).

The purpose of this review is to critically investigate the use of topical and systemic antibiotic therapy in the management of DED related to MGD or blepharitis. This review also aims to pinpoint areas of future research necessary to ensure the correct use of antibiotics in DED management.

2 Methods

A literature review was conducted on PubMed on the 15th of November 2021 using the following search term: *(antibiotics OR azithromycin OR doxycycline OR minocycline) AND (dry eye disease OR meibomian gland OR blepharitis anterior OR blepharitis posterior OR chronic blepharitis)*. Articles were limited to original research with available English full-text that investigated the effect of oral and/or topical antibiotic treatment on symptoms and/or signs of ocular surface disease in patients with DED, MGD, blepharitis, or DED related to MGD or blepharitis. Case reports, review articles, non-peer-review literature, articles with abstract only, articles only available in a non-English language, and articles on unrelated topics were excluded. A flowchart of the process can be seen in **Figure 6**.

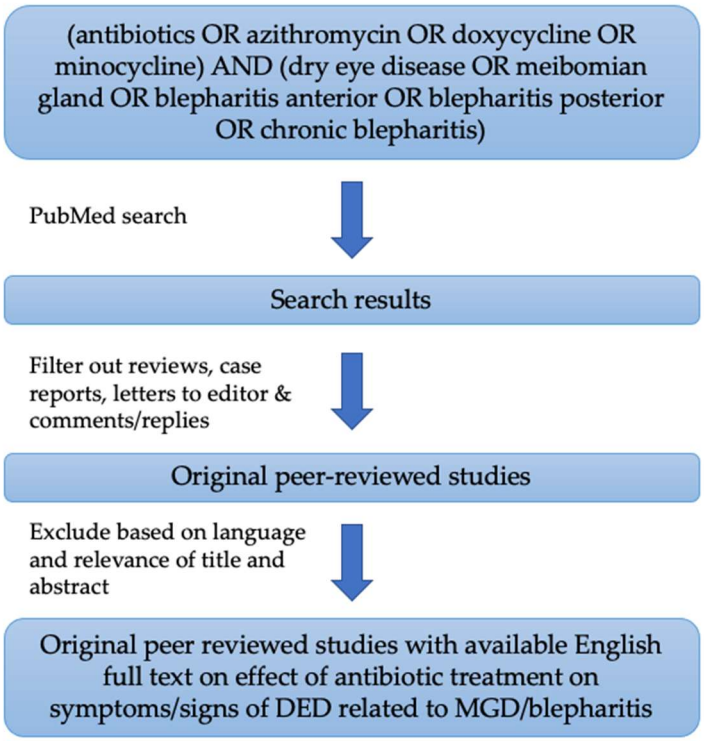


Figure 5. Flowchart of PubMed search methodology for determining studies of relevance for the present review.

To summarize the results of each article, tables were created, focusing on reported efficacy and safety outcomes. Important factors including the type of study, sample size,

patient outcomes, and key takeaways were examined in these tables. The tables were divided into subjective and objective measures and compared across articles, with special focus on controlled trials.

3 Results

3.1 Review of Existing Literature

The search term *(antibiotics OR azithromycin OR doxycycline OR minocycline) AND (dry eye disease OR meibomian gland OR blepharitis anterior OR blepharitis posterior OR chronic blepharitis)* yielded 619 articles. After excluding review articles and case reports, 311 studies were assessed for relevancy by title and abstract. At this step, 275 articles were excluded, leaving 36 articles of relevance, which were evaluated by full-text. Of these, 22 articles met the inclusion criteria and were used in the final analysis of this review based on the full-text contents. The final 22 studies included twelve randomized controlled trials (RCTs) (25, 36, 39, 40, 46-53), nine non-randomized prospective studies (41, 54-61), and one retrospective study (62). The studies were published between April 2003 (61), and January 2021 (51), and were conducted in twelve different countries: Brazil (41), USA (48, 50, 54, 55, 58-61), France (56), Spain (39), Italy (57), Turkey (49, 52, 62), Iran (40, 53), Lebanon (25), Korea (36, 46), Japan (51), and Thailand (47). A summary of the studies and their main results is shown in **Table 1** and **Table 2**. **Table 1** shows an overview of key characteristics of the included studies, while **Table 2** highlights changes in signs and symptoms from baseline to final follow-up across prospective studies.

Table 1. Summary of important characteristics of the included studies

Study	Design	Follow-up	Sample	Dose and Length of Treatment	Adjuvant Treatment	Adverse Events	Outcome
De Benedetti et al. 2019, ES (39)	Double-masked RCT, crossover	3 mo/9 mo[1]	Recalcitrant MGD (n=103)	AZ: 500 mg, d 1, 250 mg/d, d 2-5 / DC: 100 mg 2x/d w 1, 100 mg 1x/d, w 2-4	Yes	Mild GI symptoms[a] (6% AZ, 24% DC*)	Signs, but not symptoms, improved in both groups. AZ improved ocular parameters faster than DC. Retreatment and switching between groups were prevalent.
Kashkouli et al. 2015, IR (40)	Double-masked RCT	2 mo	Recalcitrant MGD (n=100)	AZ: 500 mg, d 1, 250 mg/d, d 2-5 / DC: 200 mg/d, 1 mo	Yes	Mild GI symptoms[a] (4% AZ, 26% DC*)	Signs and symptoms improved in both groups. AZ showed greater improvement than DC in some signs and had fewer adverse events.
Fadlallah et al. 2012, LB (25)	Double-masked RCT	3 mo	Moderate-to-severe BL ant and/or post (n=67)	AZd1: 1.5% 2x/d, 3 d / AZd2: 1.5% 2x/d, 3 d, 1x/d, d 4-28	Yes	Hypersensitivity[b]	A one-month AZd treatment yielded better results than a three-day treatment and was well tolerated.
Yoo et al. 2005, KR (46)	Double-masked RCT	1 mo	Recalcitrant MGD (n=150)	DC: 200 mg 2x/d, 1 mo / DC: 20 mg 2x/d, 1 mo / Placebo, 1 mo	No	Mild GI symptoms[a], hypersensitivity[c], stomatitis	Symptoms and signs (TBUT, Sch.I) improved. Low-dose DC was as effective as high-dose DC with significantly fewer adverse events (17% vs. 39% respectively).
Satitpitakul et al. 2019, TH (47)	Single-masked RCT	4 w	Moderate-to-severe MGD (n=169)	AZd: 1.5% 2x/d, 2 d, 1x/d, d 3-28 / DC: 100 mg 2x/d, 4 w	Yes	Ocular symptoms[d] (55% AZd), mild GI symptoms[a] and other symptoms[e] (20% DC)	Symptoms and signs improved in both groups, no significant difference between groups but more adverse events with AZd.
Hagen et al. 2018, US (48)	Single-masked RCT	3 mo	Moderate-to-severe MGD (n=28)	DC: 100 mg 2x/d, w 1-2, 100 mg 1x/d, w 3-13 / VTP: One LipiFlow treatment	Continued existing	Mild GI symptoms[a] (DC)	Symptoms and some clinical signs were improved in DC group. The VTP group improved significantly more.
Yildiz et al. 2018, TR (49)	Open-label RCT	9 w	BL (n=30)	AZd: 1.5% 2x/d, 3 d, 1x/d, d 4-28 / AZ: (500 mg, d 1, 250 mg 1x/d, d 2-5, drug-free, d 6-10) repeated thrice	Yes		Both treatment methods improve symptoms and signs, but topical AZd showed some superiority in improving eyelid margin changes.
Zandian et al. 2015, IR (53)	Open-label RCT	3 w	BL (n=44)	AZd: 1.0% 2x/d, 1 w, 1x/d, 2 w / DC: 100 mg 1x/d, 3 w	Yes	None (AZd), nausea (31.5% DC), vomiting and diarrhea (10.5% DC)	Both treatment methods improve symptoms, but doxycycline had better improvement in some signs. No adverse events were reported with AZd treatment.
Lee et al. 2012, KR (36)	Open-label RCT	2 mo	Moderate-to-severe MGD (n=60)	MC: 50 mg 2x/d, 2 mo + AT: 0.1% SH 4x/d, 2 mo / AT: 0.1% SH 4x/d, 2 mo	No	Mild GI symptoms[a] (MC)	Symptoms and signs improved in both groups, no significant difference in Sch.I, CSS and symptoms between groups.
Arita et al. 2021, JP (51)	Open-label RCT	2 w	MGD-associated BL post (n=36)	AZd: 1.0% 2x/d, 2 d, 1x/d, d 3-14 / AT: 0.1% PC, 0.4% SC 4x/d, 14 d	Yes	Ocular symptoms[f] (AZd), constipation (12.5% AZd)	AZd showed superiority over artificial tears in improving symptoms and signs. Adverse events of AZd did not result in discontinuation of treatment, and ocular adverse events subsided by the third day of treatment.

Ciloglu et al. 2019, TR (52)	Open-label RCT	3 mo	Severe MGD (n=85)	AZ: (500 mg 1x/d, 3 d, drug free, 7 d) repeated thrice / AZ: (same regimen) + AZd: 1.5% AZd 2x/d, 3 d, 1x/d, d 4-30	Yes		The addition of AZd to systemic AZ in conjunction with adjuvant treatment gave greater improvement in signs and symptoms than AZ alone with adjuvant treatment.
Luchs et al. 2008, US (50)	Open-label RCT	2 w	Moderate-to-severe BL (n=21)	AZd: 1.0% 2x/d, 2d 1x/d, d 3-14 / WC x2/d, 2w	Yes	Ocular symptoms[f] (5% AZd)	Symptoms and signs improved in both groups. Some signs improved significantly more in the AZd group.
Opitz et al. 2011, US (54)	Single-group prospective	4 w	BL (n=26)	AZd: 1.0% 2x/d, 2 d, 1x/d, d 3-28	Yes	Allergic conjunctivitis (4%), ocular burning (4%)	Signs and symptoms improved with AZd treatment
Haque et al. 2010, US (55)	Single-group prospective	8 w	Moderate-to-severe BL (n=23)	AZd: 1.0% 2x/d, 2 d, 1x/d, d 3-28	No	Ocular symptoms[g] (39%), unspecified (8%)	Symptoms and some clinical signs were improved, but there was worsening in TBUT.
Souchier et al. 2008, FR (56)	Controlled prospective	8 w	Recalcitrant MGD (n=20)	MC: 50 mg 2x/d, 8 w + WC / WC	Yes		MC was more effective than lid hygiene alone in increasing tear film stability and biological effect on MFA composition.
Igami et al. 2011, BR (41)	Single-group prospective	53 d	Recalcitrant BL (n=13)	AZ: (500 mg 1x/d, 3 d, drug-free, 7 d) repeated thrice	Continued existing		Improvement in some symptoms and signs.
Iovieno et al. 2009, IT (57)	Single-group prospective	1 mo	Chronic BL (n=8)	DC: 100 mg 2x/d, 2 w, 100 mg 1x/d, w 3-4	Yes	Mild GI symptoms[a] (38%), rash (13%)	Symptoms and signs improved. MMP-9 activity reduced.
Aronowicz et al. 2006, US (58)	Single-group prospective	6 mo	MGD-related DED (n=14)	MC: 50 mg 1x/d, 2 w, 100 mg 1x/d, 10 w	No	None	Improvement in most signs persisted until 3 months after discontinuation, though not all.
Shine et al. 2003, US (61)	Single-group prospective	6 mo	Chronic BL (n=10)	MC: 50 mg 1x/d, 2 w, 100 mg x1/d, until 3 mo	No	None	MC decreases MG lipid degradation products.
Foulks et al. 2010, US (59)	Single-group prospective	8 w	Recalcitrant MGD (n=17)	AZd: 1.0% 2x/d, 2 d, 1x/d, d 3-28		Ocular stinging (9%)	AZd treatment improved both symptoms and signs.
Foulks et al. 2013, US (60)	Follow-up on Foulks 2010	8 w	Recalcitrant MGD (n=31)	AZd: See Foulks 2010 / DC: 100 mg 2x/d, 2 mo		Ocular stinging (9% AZd), mild GI symptoms[a] (22% DC)	Both AZd and oral DC improved several aspects of meibum composition and quality. Most signs and symptoms also improved.
Balci et al. 2018, TR (62)	Retrospective chart review	3 mo	MGD (n=35)	AZd: 1.5% 2x/d, 2 d, 1x/d, d 3-28	Yes	Ocular stinging (14%), ocular redness (11%)	Symptoms and signs improved after 1 mo of treatment, but the improvements in signs did not persist during the 3-mo follow-up.

* = Statistically significant difference; "blank space" = not described

Abbreviations: RCT, randomized controlled trial; MG, meibomian gland; MGD, meibomian gland dysfunction; BL, blepharitis; ant, anterior; post, posterior; DED, dry eye disease; AZ, oral azithromycin; DC, oral doxycycline; VTP, vectored thermal pulsation; MC, oral minocycline; AT, artificial tears; AZd, azithromycin eyedrops; SH, sodium hyaluronate; PC, potassium chloride; SC, sodium chloride; d, day(s); w, week(s); mo, month(s); WC, warm compresses; GI, gastrointestinal; MMP-9, matrix metalloproteinase-9; TBUT, tear break-up time; Sch.I, Schirmer I test; MFA, meibomian fatty acid; CSS, conjunctival stain score

[1] = 46/103 subjects were moved between groups at the 3-month follow-up, and 37/103 were retreated at the 6-month follow-up, substantially changing group composition during the 9-month follow-up period.

[a] = nausea, diarrhea, abdominal cramp, decreased appetite; [b] = adverse events not described but one patient in AZd1 group and two patients from AZd2 group discontinued due to allergic reaction and continuous irritation, respectively; [c] = itchy skin, urticaria, erythematous papules; [d] = eye irritation, blurred vision, eyelid margin redness, eyelid edema; [e] = dizziness, rash, fever, mood change; [f] = blurred vision, eye irritation; [g] = eye pain, blurred vision, eye irritation, eye pruritus, eye discharge, vitreous detachment

Table 2. Changes in signs and symptoms between baseline and last follow-up across prospective studies

			Subjective		Standard Diagnostics				Glands, lids, and surrounding area		
Study	**Design**	**Treatment**	**Symp**	**VA**	**Sch. I**	**OSS**	**TBUT**	**Hyperemia/ Redness**	**LMA[A]**	**MGP**	**Meibum Properties**
Kashkouli et al. 2015 (40)	Double-masked RCT	AZ:	↑			↑*	↑	↑*	↑	↑	
		DC:	↑			↑	↑	↑	↑	↑	
Fadlallah et al. 2012 (25)	Double-masked RCT	AZd1:	↑						↑		↔[a]
		AZd2:	↑						↑*		↑[a]*
Yoo et al. 2005 (46)	Double-masked RCT	DC 200 mg:	↑		↑		↑				
		DC 20 mg:	↑		↑		↑				
		Placebo	↔		↔		↔				
Satitpitakul et al. 2019 (47)	Single-masked RCT	AZd:	↑			↑	↑				↑
		DC:	↑			↑	↑				↑
Hagen et al. 2018 (48)	Single-masked RCT	DC:	↑[1]			↔/↑[b]	↔				
		VTP:	↑[1]*			↑	↑				
Yildiz et al. 2018 (49)	Open-label RCT	AZd:	↑[2]		↑	↑	↔*		↑		↑
		AZ:	↑[2]		↔	↔/↑[b]	↔		↑		↑
Zandian et al. 2015 (53)	Open-label RCT	AZd:	↑		↔	↑		↑*		↑	
		DC:	↑		↔	↑*		↑		↑*	
Lee et al. 2012 (36)	Open-label RCT	MC+AT:	↑[2]		↑	↔/↑*[c]	↑*		↑*		↑*
		AT:	↑[2]		↔	↑	↑		↑		↑
Arita et al. 2021 (51)	Open-label RCT	AZd:	↑[1]*		↔	↔	↑		↑*[d]	↑*	↑*
		AT:	↑[1]		↔	↔	↔		↔[d]	↑	↔
Ciloglu et al. 2019 (52)	Open-label RCT	AZ:	↑[2]			↔	↑				↑
		AZ+AZd:	↑*[2]			↑*	↑*				↑
Luchs et al. 2008 (50)	Open-label RCT	AZd+WC:	↑	↑				↑*	↑	↑*	↑*
		WC:	↑	↑				↑	↑	↑	↑
Opitz et al. 2011 (54)	Open-label clinical trial	AZd:	↑[2]	↔	↑	↑	↑				↑
Haque et al. 2010 (55)	Open-label clinical trial	AZd:	↑	↔		↔	↑	↑		↑	

Souchier et al. 2008 (56)	Controlled prospective	MC+WC:				↔	↑				↔
		WC:				↔	↔				↔
Igami et al. 2011 (41)	Single-group prospective	AZ:	↑		↔	↔	↑	↑	↑		
Iovieno et al. 2009 (57)	Single-group prospective	DC:	↑			↑		↑	↑		
Aronowicz et al. 2006 (58)	Single-group prospective	MC:			↔	↔		↑	↑	↑	↔
Foulks et al. 2010 (59)	Single-group prospective	AZd:	↑				↑	↑	↑	↑	
Foulks et al. 2013 (60)	Follow-up on Foulks 2010	AZd:	↑				↑	↑	↑	↑*	
		DC:	↑/↔				↑	↑	↑	↔	

↑ = significant improvement at $p<0.05$; ↔ = no significant difference reported; "blank space" = not described
* = significantly greater improvement than other study arm ($p<0.05$)

Abbreviations: Symp, symptoms; VA, visual acuity; Sch. I, Schirmer I test; OSS, ocular surface staining; TBUT, tear break-up time; LMA, lid margin abnormality; MGP, meibomian gland plugging; RCT, randomized controlled trial; AZ, azithromycin; DC, doxycycline; MC, minocycline; VTP, vectored thermal pulsation; MC+WC, minocycline and eyelid hygiene and warm compresses; WC; warm compresses; MC+AT, minocycline and artificial tears; AT, artificial tears; AZd, azithromycin eyedrops; AZd1, azithromycin eyedrops for three days; AZd2, azithromycin eyedrops for one month; AZd+WC, azithromycin eye drops and warm compresses

[1] = SPEED score (Standard Patient Evaluation for Eye Dryness); [2] = OSDI (Ocular Surface Disease Index)

[A] = LMA was reported in studies as LMA, eyelid debris, eyelid swelling, eyelid hyperemia/redness, lid telangiectasia/vascularity or lid collarettes

[a] = total MGD score (sum of meibomian gland plugging and meibomian gland secretions score); [b] = Lissamine green staining improved, but fluorescein staining did not; [c] = improvement in corneal staining score but not conjunctival, Oxford, or DEWS staining score; [d] = lid vascularity

3.2 Treatment Duration and Follow-Up

The most common duration of treatment for oral antibiotics was five days for azithromycin (39-41, 49), one month for doxycycline (39, 40, 46-48, 57, 60), and three months for minocycline (36, 56, 58, 61). Topical azithromycin was most often used for four weeks (25, 47, 49, 50, 52, 54, 55, 59, 62).

Eleven studies had the final follow-up at the end of treatment (36, 46-48, 50, 51, 53, 54, 56, 57, 60). Ten other studies had a follow-up time between one week to three months after ending of treatment (25, 40, 41, 49, 52, 55, 58, 59, 61, 62). One study included follow-up of patients who responded to treatment up to eight months after the end of doxycycline treatment and up to eight months and three weeks after the end of azithromycin treatment (39).

3.3 Changes in Subjective Measures

A majority of the prospective studies that evaluated patients' symptoms used varying non-standardized symptom scores (25, 39-41, 46, 47, 50, 53, 55, 57, 59, 60). Four studies used the Ocular Surface Disease Index (OSDI) questionnaire (36, 49, 52, 54), and two studies used the SPEED score (Standard Patient Evaluation for Eye Dryness) (48, 51). Three studies did not evaluate subjective scores (56, 58, 61). Changes in subjective symptoms from baseline until last follow-up can be seen in **Table 2**.

All formulations of antibiotics were effective in alleviating subjective symptoms and no study found a greater improvement in symptoms with one formulation over another (40, 46, 47, 49, 53, 60). However, one study, on patients with severe MGD, found that symptoms improved significantly more when topical azithromycin was used in conjunction with

systemic azithromycin than systemic azithromycin alone (52). Another study, on patients with moderate-to-severe MGD, reported greater improvement in symptoms after vectored thermal pulsation (VTP) treatment than after oral doxycycline (48). No studies reported an overall worsening of subjective scores in the groups receiving antibiotic treatment, although in treatment with topical azithromycin, some of the ocular symptoms defined as adverse events could be classified as worsening of subjective symptoms (25, 47, 50-55, 59).

3.4 Changes in Objective Measures

The most frequently reported objective measures taken before and after treatment in the reviewed articles were tear film break-up time (TBUT), ocular surface staining (OSS), conjunctival hyperemia/redness, and lid margin abnormality (see **Table 2**).

Generally, there were significant short-term improvements in many of the objective measures of dry eye with oral antibiotic treatment. After treatment with oral doxycycline, TBUT improved in four (40, 46, 47, 60) out of five studies (40, 46-48, 60), Schirmer scores in one (46) out of two studies (46, 53), OSS in five (40, 47, 48, 53, 57) out of five studies (40, 47, 48, 53, 57), and conjunctival hyperemia/redness in four (40, 53, 57, 60) out of four studies (40, 53, 57, 60). In addition, improvements in lid margin abnormality were reported in three (40, 57, 60) out of three studies (40, 57, 60), meibomian gland plugging in two (40, 53) out of three studies (40, 53, 60), and meibum properties in one out of one study (47).

Oral azithromycin was also shown to be effective, with improved TBUT in three (40, 41, 52) out of four studies (40, 41, 49, 52), OSS in two (40, 49) out of four studies (40, 41, 49, 52), and conjunctival hyperemia/redness in two (40, 41) out of two studies (40, 41). Furthermore, improvements in lid margin abnormality were reported in three (40, 41, 49)

out of three studies (40, 41, 49), meibomian gland plugging in one (40) out of one study (40), and meibum properties in two out of two studies (49, 52). However, Schirmer scores did not change in either of the two studies assessing this (41, 49).

Four studies investigated the effect of oral minocycline treatment (36, 56, 58, 61), with varying results. Whereas one study reported improvement in Schirmer score (36), another did not (58). Similarly, one study reported improved OSS and meibum scores after minocycline use (36), while two studies did not (56, 58). Two out of two studies reported improvement in TBUT (36, 56), and lid margin abnormality was also found to improve in two out of two studies (36, 58). Conjunctival hyperemia/redness and meibomian gland plugging were found to improve after minocycline treatment in one out of one study (58). Shine et al. (61) investigated only the effect on meibomian gland lipids, in patients with chronic blepharitis, and found an improvement in lipid degradation products after a two-month minocycline treatment.

Of the included studies, only two RCTs compared the effect of different oral antibiotics on patients with recalcitrant MGD (39, 40). Direct comparison of the two treatments showed that azithromycin treatment was significantly more effective than doxycycline at ameliorating signs and symptoms (39). The other study reported that azithromycin gave a statistically significant greater improvement in OSS and TBUT than doxycycline (40).

Topical azithromycin was also found to give improvements in many objective measures and signs of dry eye. TBUT improved in five (47, 51, 54, 55, 59) out of six studies (47, 49, 51, 54, 55, 59), Schirmer scores in two (49, 54) out of four studies (49, 51, 53, 54), OSS in four (47, 49, 53, 54) out of six studies (47, 49, 51, 53-55), and conjunctival hyperemia in four (50, 53, 55, 59) out of four studies (50, 53, 55, 59). Additionally, lid margin abnormality

improved in five (25, 49-51, 59) out of five studies (25, 49-51, 59), and meibomian gland plugging in five (50, 51, 53, 55, 59) out of five studies (50, 51, 53, 55, 59). Meibum properties improved in five (47, 49, 50, 54) out of five studies (47, 49, 50, 54), and in one study that compared a three day topical azithromycin treatment to a one month treatment found that meibum properties only improved after treatment of one month (25). Ciloglu et al. compared the efficacy of topical azithromycin supplementation to systemic azithromycin with systemic azithromycin only, on patients with severe MGD (52). They found that the combination of topical and systemic azithromycin resulted in significantly better TBUT and OSS than systemic azithromycin alone. (52).

3.5 Changes in Signs and Symptoms From End of Treatment Until Last Control

Only eight of the 22 included studies had follow-ups both at the end of treatment and after a period without active treatment (25, 39, 40, 49, 52, 55, 58, 61). Two studies found that after a four-week treatment with topical azithromycin, on patients with blepharitis, the improvements in symptoms and signs did not decline at four (55) or five weeks (49) following the discontinuation of active treatment. Another study found that two months after the end of a one-month treatment with topical azithromycin in supplementation to systemic azithromycin, in patients with severe MGD, the improvements in signs and symptoms remained improved (52). One study that compared a three-day treatment with topical azithromycin to a one-month treatment, in patients with moderate-to-severe anterior or posterior blepharitis, reported that the improvement in symptoms, and some, but not all signs remained improved until two months and 24 days after end of an active three-day treatment (25). On the other hand, all improvements persisted until two months after the

end of a one-month topical azithromycin treatment (25). Following three months of oral minocycline treatment in patients with MGD-related DED, one study reported that the ocular parameters that were improved after treatment, remained improved for the three following months (58). Another study reported that lipid degradation products remained improved three months after the end of active treatment in a similar three-month minocycline regime on patients with chronic blepharitis (61). After oral azithromycin treatment on blepharitis patients, improvements in some, but not all signs persisted until five weeks after the end of treatment (49). Another study on patients with recalcitrant MGD reported that improvements in all signs and symptoms persisted until almost eight weeks after the end of a five-day oral azithromycin treatment (40), as well as one month after discontinuation of a one-month oral doxycycline treatment (40).

3.6 Type of Antibiotics

The two RCTs that directly compared oral azithromycin and oral doxycycline in recalcitrant MGD treatment (39, 40) both assessed the effect of a five-day treatment course of oral azithromycin and a one-month treatment course of oral doxycycline. These studies found that azithromycin achieved a significantly greater improvement in some of the ocular parameters than doxycycline, with a shorter treatment course, and lower rates of adverse events. De Benedetti et al. followed the subjects over nine months and found that significantly more patients in the azithromycin group were stable after only one treatment than those in the doxycycline group, 83% and 34%, respectively (39). Additionally, fewer participants receiving azithromycin (17%) than those receiving doxycycline (66%) needed repeated treatments, and the azithromycin group had a higher improvement rate, with only

6% of patients not improving, compared with 29% in the doxycycline group. Kashkouli et al. (40) found that azithromycin resulted in significantly greater improvement in some ocular parameters than doxycycline, but the study had a short follow-up time of under two months.

3.7 Adverse Events

The most frequently reported adverse events of oral doxycycline treatment were GI symptoms (39, 40, 46-48, 53, 57, 60). Rashes (47, 57), dizziness, fever, mood change (47), hypersensitivity, and stomatitis (46) were also reported. The reported prevalence of these adverse events is given in **Table 1**. GI symptoms were reported in one (36) of four studies investigating the effect of oral minocycline (36, 56, 58, 61). With oral azithromycin treatment, GI symptoms were also the most commonly reported adverse events (39, 40). With topical azithromycin treatment, ocular symptoms, such as ocular stinging or irritation, blurred vision, and ocular redness or eyelid edema were frequently reported (47, 50, 51, 54, 55, 59, 62). The two studies that compared oral doxycycline and azithromycin treatments found GI symptoms to be more frequent with doxycycline (39, 40).

4 Discussion

4.1 Unclear Long-Term Benefits of Antibiotic Treatment

Based on the reviewed material, both topical and systemic antibiotics appear to have substantial short-term benefits when used to manage DED related to MGD or blepharitis. However, diminishing positive effects with time after completed treatment were also reported (25, 39, 49). Evidence for long-term positive effect was found to be weak, as only eight of the 21 prospective studies had a follow-up both at the end of treatment and after a

period following discontinuation (25, 39, 40, 49, 52, 55, 58, 61). The majority of these studies had the last follow-up of only three months or less after end of active treatment (25, 40, 49, 52, 55, 58, 61). One study reported that antibiotic treatments were frequently repeated with some patients not showing improvement despite repeated treatments, making the long-term benefits of antibiotic treatment in patients with recalcitrant MGD unclear (39). Assessing long-term effects is especially important for oral antibiotics, where treatment often consists of one to three months of tetracyclines (10, 11, 45), or three times three days of high-dose azithromycin (11). Oral antibiotics can disrupt the gut microbiome (63), and cause resistance development (64). It is essential that the benefits of the antibiotic use last beyond the active treatment period itself, as uncritical use of broad-spectrum antibiotics has the potential to do great harm. Blepharitis and MGD are very common ocular disorders, affecting hundreds of millions of people (1, 19, 31). High-level evidence for the long-term benefits of oral antibiotics for MGD and blepharitis is essential for guiding clinical practice.

4.2 Effects During Drug-Free Intervals

The included studies found a therapeutic effect of antibiotics on symptoms, and many of the objective measures, during active treatment. However, around half of the prospective studies did not have follow-ups after the end of active treatment (36, 46-48, 50, 51, 53, 54, 56, 57). In the prospective studies with prolonged follow-up after the end of active treatment, mixed results were found (25, 39-41, 49, 52, 55, 58, 59, 61). Most of these studies only followed their patients for between one week and three months after completed treatment (25, 40, 41, 49, 52, 55, 58, 59, 61). In the study with the longest follow-up, the follow-up time did not qualify as eight months for a big part of the participants, as the treatment plan for many participants changed throughout the study period (39). Only those with "good" or

"excellent" response to the first antibiotic treatment were not retreated and thus had eight months between end of active treatment and last follow-up. In order to better provide evidence of the long-term benefit of antibiotic treatment, more level I studies with prolonged follow-up time are needed.

4.3 Lower Dosage of Tetracyclines Should be Considered

An important finding of this review is that placebo-controlled studies are mostly missing. There was only one study on patients with recalcitrant MGD that compared antibiotic treatment to placebo (46).

Several different treatment regimens and dosages of oral antibiotics were used in the included studies. Guidelines recommend using oral tetracyclines for three months at a relatively low dose, but do not specify the dosage (10). The ideal dosing schedule of tetracyclines in the treatment of DED related to MGD and/or blepharitis remains to be established (11), and many dosing regimens have been suggested, ranging from 50 or 100 mg doxycycline once a day to 200 mg twice daily for one month followed by 200 mg daily (11). One of the included studies compared the effects of 20 mg and 200 mg of doxycycline twice daily on patients with recalcitrant MGD, to placebo (46). The authors found both dosages to perform better compared to placebo and were equally effective at reducing signs and symptoms of dry eye. Fewer adverse events were reported in the low-dose group. This could indicate that the commonly used dosages of oral doxycycline could be substantially decreased, and adverse events reduced, while maintaining the clinical effect on dry eye. Furthermore, long-term doxycycline treatment of 40 mg or less daily does not seem to exert antibiotic selection pressure on the microbiota, thereby minimizing the chances of antibiotic resistance development (65, 66). Many practitioners may prescribe high dosage antibiotics

such as doxycycline in the treatment of DED related to MGD or blepharitis due to doxycycline's well-known role in rosacea treatment (67). Conventional use of tetracycline agents such as doxycycline and minocycline in rosacea treatment are dosages of 100 to 200 mg daily (67). Reducing the total antibiotic usage is an important measure to limit antibiotic resistance development (68, 69). Further research on the effect of low-dose antibiotics in the treatment of DED related to MGD or blepharitis, and their impact on antibiotic resistance bacteria, could be helpful for establishing guidelines with well-defined dosage recommendations.

4.4 The Paradoxical Effects of Antibiotics on Ocular Inflammation

In addition to direct antibacterial effects, the antibiotics used in DED treatment are known to have anti-inflammatory properties (11, 13). Inflammation is an important factor in blepharitis- and MGD-related DED, and effective treatment should target this (70). Iovieno et al. (57) found that four weeks of oral doxycycline in the treatment of chronic blepharitis reduced the activity of the inflammatory marker MMP-9 in tears. Increased MMP-9 activity is implicated in the development and maintenance of DED (71), and as tetracyclines blunt MMP-9 expression (72) this reduction could explain doxycycline's effect on chronic idiopathic blepharitis. This is in line with findings on tetracyclines, which are found to reduce the activity and production of collagenases, phospholipases, MMPs, interleukin-1 (IL-1), and tumor necrosis factor alpha (TNF-α) in many tissues, including the corneal epithelium (11, 71, 73, 74). Additionally, tetracyclines decrease bacteria-produced lipolytic exoenzymes and inhibit lipase production, slowing the build-up of meibomian lipid breakdown products (61, 75, 76). These factors likely contribute to the improvement seen when tetracyclines are prescribed to treat blepharitis- and MGD-associated DED.

Paradoxically, antibiotic use has also been shown to initiate local inflammation and impair innate anti-inflammatory capabilities through disruption of the native ocular microbiome (29). Furthermore, upsetting the natural microbiome of the gut with antibiotics has been shown to cause DED in laboratory animals (77), and the gut microbiome has been implicated in a pathophysiological pathway that may lead to DED (78). Further research comparing the effects of antibiotics with anti-inflammatory properties to anti-inflammatory drugs without antibacterial properties could provide useful insights. Analysis of the bacterial species composition of the ocular microbiome in addition to the regular clinical assessment tests may also be an important strategy when deciding and monitoring treatment of MGD and should be considered in future trials.

4.5 The Importance of an Improved Meibum Quality and Lipid Layer

As thickened and stagnant meibum plays an important role in the development of DED related to MGD and posterior blepharitis (3), it is crucial to focus treatment on improving meibomian gland status and lipid layer stability. A single VTP therapy was found to achieve greater improvement in some clinical signs of dry eye than a three-month doxycycline treatment, in one study (48). VTP treatment is costly but may have fewer systemic adverse events than doxycycline and does not contribute to antibiotic resistance. One study on patients with MGD-associated posterior blepharitis reported that treatment with topical azithromycin yielded greater improvements in symptoms and some signs of DED compared to artificial tears (51), although adverse events were more common in the azithromycin group. More studies are needed to compare the effectiveness of VTP and other drug-free treatments to the use of antibiotics. Furthermore, one study found that minocycline combined with warm compresses and lid hygiene was superior to warm compresses and lid

hygiene alone in improving tear film stability among patients with recalcitrant MGD (56), and another study on patients with moderate-to-severe MGD reported that minocycline treatment concurrent with artificial tears yielded a greater improvement than artificial tears alone (36). This suggests that antibiotic treatment has an enhanced effect on MGD-related DED when used together with adjuvant treatment, although more high-level evidence is needed.

4.6 Topical vs. Systemic Antibiotic Treatment; Risks and Benefits

Topical antibiotic treatment comes without many of the negative side-effects associated with systemic use. Topical azithromycin may reduce meibomian gland inflammation and lower the transition temperature of the meibum (79). None of the included studies comparing topical azithromycin treatment with systemic treatment found systemic antibiotics to outperform topical (47, 49, 53, 60). In fact, across four articles (47, 49, 53, 60), topical treatment showed as good or better effect than systemic antibiotic treatment. However, it is not certain whether the improvement in signs and symptoms achieved with topical azithromycin persist after discontinued treatment (62). Additionally, studies comparing topical azithromycin treatment with oral doxycycline report mixed results regarding adverse events (47, 53, 60). Minor adverse events were more common with topical azithromycin in one study (47), while in two other studies, it occurred more often with oral doxycycline treatment (53, 60). Adverse events leading to discontinued treatment were either similar between the two treatment options (47), or more common for doxycycline treatment (53). Adverse events with topical azithromycin were mainly local (25, 47, 50, 51, 53-55, 59, 62), and the drug is not detectable in blood at appropriate doses (42). However, the eye drops in five of the studies using topical azithromycin treatment contained preservatives

(50, 53-55, 59), which is important to keep in mind, as the preservatives alone can lead to adverse ocular events (80). Overall, in treatment of MGD and blepharitis, topical and systemic antibiotic use appeared to have similar effect (47, 49, 53, 60), which is in line with previous findings comparing topical and oral azithromycin in MGD treatment (17). Thus, topical antibiotics may be a viable alternative treatment to reduce the amount of antibiotics used. However, further RCTs comparing the long-term effects of these two treatment alternatives are needed.

4.7 Doxycycline vs. Azithromycin; Effects and Profiles

In patients with recalcitrant MGD, oral azithromycin outperformed oral doxycycline in the two studies that compared these treatments; symptoms and some signs improved quicker, and effects lasted longer than following doxycycline treatment (39, 40). Azithromycin yielded fewer adverse events (39, 40), and fewer patients needed additional treatments (39). Considering that oral azithromycin is administered for only a few days, compared to weeks to months for doxycycline, it is tempting to think that this presents another opportunity to reduce antibiotic use. However, azithromycin is particularly likely to contribute to resistance development due to its long half-life of up to three days (42).

Unlike tetracyclines, azithromycin acts directly on human meibomian gland epithelial cells to stimulate their function, leading to increased lipid accumulation and promotion of terminal differentiation of the cells (81). This stimulatory effect on human meibomian gland epithelial cell function is thought to contribute to azithromycin's greater effectiveness compared to doxycycline in treating MGD and associated evaporative DED (81). More studies with long-term follow-up comparing oral azithromycin to oral tetracyclines such as doxycycline could be useful.

4.8 Safety Analysis of Antibiotic Treatment in DED

Antibiotics were generally safe to use in patients with DED related to MGD and blepharitis. Mild adverse events were common in the included studies, but severe adverse events leading to discontinuation of treatment were rare (25, 36, 39, 46-48, 54, 57, 59). Mild GI symptoms were the most frequent adverse events in oral antibiotic treatment (36, 39, 40, 46-48, 53, 57, 60), with most studies reporting it in 13-39% of patients (39, 40, 46, 47, 53, 57, 60). However, two studies reported mild GI symptoms in only 4-9% of patients (39, 40). Local adverse events were common with topical treatment (47, 50, 54, 55, 59, 62), with most studies reporting it in 4-14% of patients (50, 54, 59, 62), although one study reported local adverse events in 55% of cases (47).

4.9 Future Directions

Uncritical use of broad-spectrum antibiotics has the potential to do great harm. Further prospective, double-blinded, placebo-controlled RCTs with a long follow-up time, assessing time-to-recurrence and the effects of repeated rounds of treatment on DED parameters, would provide useful insights on the optimal use of antibiotics in the treatment of DED related to MGD and blepharitis. In addition, future research comparing different antibiotic options, as well as comparing antibiotic treatment to other, non-medical treatment options are needed.

4.10 Limitations

One limitation in the literature examined for this review was the short follow-ups reported in many of the studies. The longest follow-up time was just under nine months after active treatment; however, this only applied to patients with "good" or "excellent" response to the initial treatment (39). This made the assessment of the long-term effect of antibiotic

treatment of DED related to MGD or blepharitis difficult. A further limitation was the variation in symptom scoring used across the studies. Only six studies (36, 48, 49, 51, 52, 54) used standardized questionnaires, with OSDI being the most frequently used (36, 49, 52, 54). The majority of studies used various non-standardized symptom scores (25, 39-41, 46, 47, 50, 53, 55, 57, 59, 60). Further limitations are the uncontrolled use of adjuvant treatments, and unknown compliance of taking the antibiotics. Differences in study duration, design, and grading systems made direct comparison across studies more challenging, making a meta-analysis therefore not possible to carry out.

5 Conclusion

Current evidence suggests that topical and oral antibiotic use in managing DED related to MGD or blepharitis yields short-term improvement in signs and symptoms, but the long-term effects are still unclear. Given the large number of patients suffering from these conditions, and the rising problem of antibiotic resistant bacteria, the role of antibiotic use in DED management and the potential harm of overuse of antibiotics in the long-term should be carefully considered, particularly given the availability of other purely anti-inflammatory or non-medicinal alternative treatments. A survival-analysis of a single round of antibiotics, in addition to the effects of repeated rounds of treatment, on DED parameters could add useful information on the long-term effects.

6 Disclosure

Ragnheiður Ravnaas Vernharðsdóttir declares no conflicts of interest.

Morten S. Magno declares no conflicts of interest.

Leif Hynnekleiv declares no conflicts of interest.

Neil Lagali declares no conflicts of interest.

Darlene A. Dartt declares no conflicts of interest.

Jelle Vehof declares no conflicts of interest.

Catherine J. Jackson declares no conflicts of interest.

Tor Paaske Utheim is co-founder and co-owner of The Norwegian dry eye clinic and the Clinic of eye health, Oslo, Norway, which delivers talks for and/or receives financial support from the following: ABIGO, Alcon, Allergan, AMWO, Bausch&Lomb, Bayer, European school for advanced studies in ophthalmology, InnZ Medical, Medilens Nordic, Medistim, Novartis, Santen, Specsavers, Shire Pharmaceuticals and Thea Laboratories. He has served on the global scientific advisory board for Novartis and Alcon as well as the European advisory board for Shire Pharmaceuticals. Utheim is the Norwegian Global Ambassador for Tear Film and Ocular Surface Society (TFOS), a Board Member of the International Ocular Surface Society, an International Member of the Japanese Lid and Meibomian gland working group (LIME), a Consultant at the Norwegian Association for the Blind and Partially Sighted, the President of the Oslo Society of ophthalmology, and the Editor-in-Chief of Oftalmolog, an eye journal distributed to all eye doctors in the Nordic region since 1980. Besides publishing articles of presumed interest to our readers, Oftalmolog publishes advertisements from pharmaceutical companies, companies selling ophthalmological equipment, and associations organizing conferences and events in ophthalmology. For more information, visit: oftalmolog.com.

7 References

1. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011;52(4):2050-64.
2. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II Epidemiology Report. The ocular surface. 2017;15(3):334-65.
3. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. The ocular surface. 2017;15(3):438-510.
4. Sullivan DA, Rocha EM, Aragona P, Clayton JA, Ding J, Golebiowski B, et al. TFOS DEWS II Sex, Gender, and Hormones Report. The ocular surface. 2017;15(3):284-333.
5. Uchino M, Yokoi N, Uchino Y, Dogru M, Kawashima M, Komuro A, et al. Prevalence of dry eye disease and its risk factors in visual display terminal users: the Osaka study. Am J Ophthalmol. 2013;156(4):759-66.
6. United Nations DoEaSA, Population Division. World Population Ageing 2019: Highlights 2019 [Available from: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf.
7. Wong CW, Tsai A, Jonas JB, Ohno-Matsui K, Chen J, Ang M, et al. Digital Screen Time During the COVID-19 Pandemic: Risk for a Further Myopia Boom? Am J Ophthalmol. 2020;223:333-7.
8. Morthen MK, Magno MS, Utheim TP, Snieder H, Hammond CJ, Vehof J. The physical and mental burden of dry eye disease: A large population-based study investigating the relationship with health-related quality of life and its determinants. The ocular surface. 2021;21:107-17.
9. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. Cornea. 2011;30(4):379-87.
10. Bowling B, Kanski JJ. Kanski's clinical ophthalmology : a systematic approach. Eighth Edition ed2016.
11. Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II Management and Therapy Report. The ocular surface. 2017;15(3):575-628.
12. Antibiotic Resistance 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance.
13. Wladis EJ, Bradley EA, Bilyk JR, Yen MT, Mawn LA. Oral Antibiotics for Meibomian Gland-Related Ocular Surface Disease: A Report by the American Academy of Ophthalmology. Ophthalmology. 2016;123(3):492-6.
14. Sabeti S, Kheirkhah A, Yin J, Dana R. Management of meibomian gland dysfunction: a review. Surv Ophthalmol. 2020;65(2):205-17.
15. Lam PY, Shih KC, Fong PY, Chan TCY, Ng AL, Jhanji V, et al. A Review on Evidence-Based Treatments for Meibomian Gland Dysfunction. Eye & contact lens. 2020;46(1):3-16.
16. Villani E, Marelli L, Dellavalle A, Serafino M, Nucci P. Latest evidences on meibomian gland dysfunction diagnosis and management. The ocular surface. 2020;18(4):871-92.
17. Tao T, Tao L. Systematic review and meta-analysis of treating meibomian gland dysfunction with azithromycin. Eye (Lond). 2020;34(10):1797-808.

18. Nelson JD, Shimazaki J, Benitez-del-Castillo JM, Craig JP, McCulley JP, Den S, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci. 2011;52(4):1930-7.
19. Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci. 2011;52(4):1938-78.
20. Nichols KK, Foulks GN, Bron AJ, Glasgow BJ, Dogru M, Tsubota K, et al. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci. 2011;52(4):1922-9.
21. Gutgesell VJ, Stern GA, Hood CI. Histopathology of meibomian gland dysfunction. Am J Ophthalmol. 1982;94(3):383-7.
22. Liu S, Richards SM, Lo K, Hatton M, Fay A, Sullivan DA. Changes in gene expression in human meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011;52(5):2727-40.
23. Kheirkhah A, Kobashi H, Girgis J, Jamali A, Ciolino JB, Hamrah P. A randomized, sham-controlled trial of intraductal meibomian gland probing with or without topical antibiotic/steroid for obstructive meibomian gland dysfunction. The ocular surface. 2020;18(4):852-6.
24. Suzuki T. Inflamed Obstructive Meibomian Gland Dysfunction Causes Ocular Surface Inflammation. Invest Ophthalmol Vis Sci. 2018;59(14):Des94-des101.
25. Fadlallah A, Rami HE, Fahd D, Dunia I, Bejjani R, Chlela E, et al. Azithromycin 1.5% ophthalmic solution: efficacy and treatment modalities in chronic blepharitis. Arq Bras Oftalmol. 2012;75(3):178-82.
26. Huber-Spitzy V, Baumgartner I, Böhler-Sommeregger K, Grabner G. Blepharitis--a diagnostic and therapeutic challenge. A report on 407 consecutive cases. Graefes Arch Clin Exp Ophthalmol. 1991;229(3):224-7.
27. Dartt DA, Willcox MD. Complexity of the tear film: importance in homeostasis and dysfunction during disease. Exp Eye Res. 2013;117:1-3.
28. St Leger AJ, Desai JV, Drummond RA, Kugadas A, Almaghrabi F, Silver P, et al. An Ocular Commensal Protects against Corneal Infection by Driving an Interleukin-17 Response from Mucosal γδ T Cells. Immunity. 2017;47(1):148-58.e5.
29. Kugadas A, Christiansen SH, Sankaranarayanan S, Surana NK, Gauguet S, Kunz R, et al. Impact of Microbiota on Resistance to Ocular Pseudomonas aeruginosa-Induced Keratitis. PLoS Pathog. 2016;12(9):e1005855.
30. Kang Y, Lin S, Ma X, Che Y, Chen Y, Wan T, et al. Strain heterogeneity, cooccurrence network, taxonomic composition and functional profile of the healthy ocular surface microbiome. Eye Vis (Lond). 2021;8(1):6.
31. Lindsley K, Matsumura S, Hatef E, Akpek EK. Interventions for chronic blepharitis. The Cochrane database of systematic reviews. 2012;2012(5):Cd005556.
32. Tavakoli A, Flanagan JL. The Case for a More Holistic Approach to Dry Eye Disease: Is It Time to Move beyond Antibiotics? Antibiotics (Basel). 2019;8(3).
33. Ainslie D. The treatment of blepharitis. Br Med J. 1951;2(4731):582-4.
34. Nelson ML, Levy SB. The history of the tetracyclines. Ann N Y Acad Sci. 2011;1241:17-32.
35. Bahrami F, Morris DL, Pourgholami MH. Tetracyclines: drugs with huge therapeutic potential. Mini Rev Med Chem. 2012;12(1):44-52.

36. Lee H, Min K, Kim EK, Kim TI. Minocycline controls clinical outcomes and inflammatory cytokines in moderate and severe meibomian gland dysfunction. Am J Ophthalmol. 2012;154(6):949-57.e1.
37. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev. 2001;65(2):232-60 ; second page, table of contents.
38. Greene JB, Jeng BH, Fintelmann RE, Margolis TP. Oral azithromycin for the treatment of meibomitis. JAMA Ophthalmol. 2014;132(1):121-2.
39. De Benedetti G, Vaiano AS. Oral azithromycin and oral doxycycline for the treatment of Meibomian gland dysfunction: A 9-month comparative case series. Indian J Ophthalmol. 2019;67(4):464-71.
40. Kashkouli MB, Fazel AJ, Kiavash V, Nojomi M, Ghiasian L. Oral azithromycin versus doxycycline in meibomian gland dysfunction: a randomised double-masked open-label clinical trial. Br J Ophthalmol. 2015;99(2):199-204.
41. Igami TZ, Holzchuh R, Osaki TH, Santo RM, Kara-Jose N, Hida RY. Oral azithromycin for treatment of posterior blepharitis. Cornea. 2011;30(10):1145-9.
42. Kagkelaris KA, Makri OE, Georgakopoulos CD, Panayiotakopoulos GD. An eye for azithromycin: review of the literature. Ther Adv Ophthalmol. 2018;10:2515841418783622.
43. Shutter MC, Akhondi H. Tetracycline. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2020, StatPearls Publishing LLC.; 2020.
44. Patel PH, Hashmi MF. Macrolides. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2020, StatPearls Publishing LLC.; 2020.
45. Ehler J, CP S. Wills Eye Manual. Office and Emergency Room Diagnose and Treatment of Eye Disease. 2008.
46. Yoo SE, Lee DC, Chang MH. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. Korean J Ophthalmol. 2005;19(4):258-63.
47. Satitpitakul V, Ratanawongphaibul K, Kasetsuwan N, Reinprayoon U. Efficacy of azithromycin 1.5% eyedrops vs oral doxycycline in meibomian gland dysfunction: a randomized trial. Graefes Arch Clin Exp Ophthalmol. 2019;257(6):1289-94.
48. Hagen KB, Bedi R, Blackie CA, Christenson-Akagi KJ. Comparison of a single-dose vectored thermal pulsation procedure with a 3-month course of daily oral doxycycline for moderate-to-severe meibomian gland dysfunction. Clin Ophthalmol. 2018;12:161-8.
49. Yildiz E, Yenerel NM, Turan-Yardimci A, Erkan M, Gunes P. Comparison of the Clinical Efficacy of Topical and Systemic Azithromycin Treatment for Posterior Blepharitis. J Ocul Pharmacol Ther. 2018;34(4):365-72.
50. Luchs J. Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis. Adv Ther. 2008;25(9):858-70.
51. Arita R, Fukuoka S. Efficacy of Azithromycin Eyedrops for Individuals With Meibomian Gland Dysfunction-Associated Posterior Blepharitis. Eye & contact lens. 2021;47(1):54-9.
52. Ciloglu E, Özcan AA, Incekalan T, Unal F. The Role of Topical Azithromycin in the Treatment of Meibomian Gland Dysfunction. Cornea. 2020;39(3):321-4.
53. Zandian M, Rahimian N, Soheilifar S. Comparison of therapeutic effects of topical azithromycin solution and systemic doxycycline on posterior blepharitis. Int J Ophthalmol. 2016;9(7):1016-9.

54. Opitz DL, Tyler KF. Efficacy of azithromycin 1% ophthalmic solution for treatment of ocular surface disease from posterior blepharitis. Clin Exp Optom. 2011;94(2):200-6.
55. Haque RM, Torkildsen GL, Brubaker K, Zink RC, Kowalski RP, Mah FS, et al. Multicenter open-label study evaluating the efficacy of azithromycin ophthalmic solution 1% on the signs and symptoms of subjects with blepharitis. Cornea. 2010;29(8):871-7.
56. Souchier M, Joffre C, Grégoire S, Bretillon L, Muselier A, Acar N, et al. Changes in meibomian fatty acids and clinical signs in patients with meibomian gland dysfunction after minocycline treatment. Br J Ophthalmol. 2008;92(6):819-22.
57. Iovieno A, Lambiase A, Micera A, Stampachiacchiere B, Sgrulletta R, Bonini S. In vivo characterization of doxycycline effects on tear metalloproteinases in patients with chronic blepharitis. Eur J Ophthalmol. 2009;19(5):708-16.
58. Aronowicz JD, Shine WE, Oral D, Vargas JM, McCulley JP. Short term oral minocycline treatment of meibomianitis. Br J Ophthalmol. 2006;90(7):856-60.
59. Foulks GN, Borchman D, Yappert M, Kim SH, McKay JW. Topical azithromycin therapy for meibomian gland dysfunction: clinical response and lipid alterations. Cornea. 2010;29(7):781-8.
60. Foulks GN, Borchman D, Yappert M, Kakar S. Topical azithromycin and oral doxycycline therapy of meibomian gland dysfunction: a comparative clinical and spectroscopic pilot study. Cornea. 2013;32(1):44-53.
61. Shine WE, McCulley JP, Pandya AG. Minocycline effect on meibomian gland lipids in meibomianitis patients. Exp Eye Res. 2003;76(4):417-20.
62. Balci O, Gulkilik G. Assessment of efficacy of topical azithromycin 1.5 per cent ophthalmic solution for the treatment of meibomian gland dysfunction. Clin Exp Optom. 2018;101(1):18-22.
63. Ferrer M, Méndez-García C, Rojo D, Barbas C, Moya A. Antibiotic use and microbiome function. Biochem Pharmacol. 2017;134:114-26.
64. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016;4(2).
65. Del Rosso JQ. A status report on the use of subantimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. Cutis. 2004;74(2):118-22.
66. Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol. 2003;139(4):459-64.
67. Valentín S, Morales A, Sánchez JL, Rivera A. Safety and efficacy of doxycycline in the treatment of rosacea. Clin Cosmet Investig Dermatol. 2009;2:129-40.
68. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, et al. Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist. 2018;11:1645-58.
69. Zaman SB, Hussain MA, Nye R, Mehta V, Mamun KT, Hossain N. A Review on Antibiotic Resistance: Alarm Bells are Ringing. Cureus. 2017;9(6):e1403.
70. Stern ME, Schaumburg CS, Pflugfelder SC. Dry eye as a mucosal autoimmune disease. Int Rev Immunol. 2013;32(1):19-41.
71. De Paiva CS, Corrales RM, Villarreal AL, Farley WJ, Li DQ, Stern ME, et al. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. Exp Eye Res. 2006;83(3):526-35.
72. Jamerson EC, Elhusseiny AM, ElSheikh RH, Eleiwa TK, El Sayed YM. Role of Matrix Metalloproteinase 9 in Ocular Surface Disorders. Eye & contact lens. 2020;46 Suppl 2:S57-s63.

73. De Paiva CS, Corrales RM, Villarreal AL, Farley W, Li DQ, Stern ME, et al. Apical corneal barrier disruption in experimental murine dry eye is abrogated by methylprednisolone and doxycycline. Invest Ophthalmol Vis Sci. 2006;47(7):2847-56.
74. Solomon A, Rosenblatt M, Li DQ, Liu Z, Monroy D, Ji Z, et al. Doxycycline inhibition of interleukin-1 in the corneal epithelium. Invest Ophthalmol Vis Sci. 2000;41(9):2544-57.
75. Ta CN, Shine WE, McCulley JP, Pandya A, Trattler W, Norbury JW. Effects of minocycline on the ocular flora of patients with acne rosacea or seborrheic blepharitis. Cornea. 2003;22(6):545-8.
76. Dougherty JM, McCulley JP, Silvany RE, Meyer DR. The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci. Invest Ophthalmol Vis Sci. 1991;32(11):2970-5.
77. Ozkan J, Willcox MD. The Ocular Microbiome: Molecular Characterisation of a Unique and Low Microbial Environment. Curr Eye Res. 2019;44(7):685-94.
78. Moon J, Yoon CH, Choi SH, Kim MK. Can Gut Microbiota Affect Dry Eye Syndrome? Int J Mol Sci. 2020;21(22).
79. Nichols JJ, Bickle KM, Zink RC, Schiewe MD, Haque RM, Nichols KK. Safety and efficacy of topical azithromycin ophthalmic solution 1.0% in the treatment of contact lens-related dry eye. Eye & contact lens. 2012;38(2):73-9.
80. Baudouin C, Labbé A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010;29(4):312-34.
81. Liu Y, Kam WR, Ding J, Sullivan DA. Can tetracycline antibiotics duplicate the ability of azithromycin to stimulate human meibomian gland epithelial cell differentiation? Cornea. 2015;34(3):342-6.