

Dysbiosis of the ocular surface – a new risk factor for ophthalmic diseases? The role of eyelid hygiene



Janusz Skrzypecki^{1,2}

¹ Department and Clinic of Ophthalmology, the Independent Public Clinical Ophthalmology Hospital, Medical University of Warsaw
Head: prof. Jacek P. Szaflik, MD, PhD

² Department of Experimental and Clinical Physiology, Medical University of Warsaw
Head: prof. Marcin Ufnal, MD, PhD

HIGHLIGHTS

The publication presents a review of data on the relationship between dysbiosis and ocular surface diseases and recommendations for the treatment of dysbiosis, including eyelid margin hygiene.

ABSTRACT

Quantitative and qualitative disturbances in the composition of the ocular surface microbiome can be a significant risk factor for the development of various ophthalmic disorders, including eyelid inflammation, dry eye syndrome, and allergic conjunctivitis. In this publication, we present a review of the data regarding the association between dysbiosis and these mentioned clinical conditions. Additionally, we provide recommendations for the treatment of dysbiosis, including eyelid hygiene.

Key words: eyelid hygiene, allergic conjunctivitis, blepharitis, dry eye

INTRODUCTION

Recently, physicians and researchers have paid a lot of attention to the qualitative and quantitative analysis of the microbiome [1]. Many studies indicate that an imbalance in the composition of normal physiological flora may be associated with the pathophysiology of many diseases, including cardiovascular, neurological or hematological diseases [2]. Moreover, the role of the microbiome seems to be important in the pathogenesis of ophthalmic diseases. The literature indicates that ocular surface dysbiosis may affect development of blepharitis, corneal ulcers, dry eye syndrome, or postoperative infections [3].

NORMAL PHYSIOLOGICAL FLORA OF THE EYELID MARGIN AND THE CONJUNCTIVAL SAC

The physiological flora of the lid margin and conjunctival sac is primarily composed of coagulase-negative staphylococci (60%), including *Staphylococcus epidermidis*. Strains of *Corynebacterium*, *Micrococcus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* occur significantly less frequently and generally do not account for more than 5–6% of the healthy microbiome [4]. The most commonly isolated fungi are *Aspergillus* or *Candida* species [5]. Moreover, it has been shown that viruses also constitute the ocular surface microbiome, but their importance remains unknown [6]. Moreover, it has been emphasized that *Demodex* spp. including *Demodex folliculorum* and *Demodex brevis*, affect the ocular surface microbiome. *Demodex folliculorum* resides primarily in hair follicles, whereas *Demodex brevis* is generally found in the sebaceous glands [7]. The total composition of the ocular microbiota is difficult to characterize due to the methodological limitations. Depending on the method used, researchers obtain varying qualitative and quantitative results. Culture-based methods and rRNA sequencing are the most common. The drawback of the first method is its lower sensitivity, whereas genetic testing is susceptible to contamination. Moreover, the composition of the ocular microbiome differs depending on the collection method (conjunctival swab, conjunctival biopsy or corneal epithelial biopsy). Therefore, due to the lack of a uniform methodology, it is challenging to compare study results and assess treatment response [8].

DYSBIOSIS OF THE OCULAR SURFACE MICROBIOME IN THE COURSE OF OPHTHALMIC DISEASES

Although numerous cross-sectional studies indicate that ocular surface dysbiosis accompanies many ophthalmic diseases, this cause-and-effect relationship has not yet been confirmed. Nevertheless, modification of the microbiome with antibiotics, antiseptics or lid margin hygiene helps improve dry eye syndrome or blepharitis symptoms. The role of lid

microbiome reduction to prevent postoperative infections or, e.g., after intravitreal injections, has been gaining popularity.

Blepharitis

Blepharitis can be divided into anterior and posterior blepharitis. Anterior blepharitis is associated with inflammation on the eyelashes, whereas the posterior variant involves meibomian gland dysfunction and inflammation of the eyelid margin. The studies have shown that in anterior and posterior blepharitis the proportion of bacterial species on the ocular surface microbiome shifts and their number increases. Some authors report that patients with blepharitis have decreased populations of *Staphylococcus* spp. and *Bacteroides* spp., and increased populations of *Lactobacillus* spp. or *Propionibacterium* spp. [9]. Moreover, an increased population of *Demodex* spp. has been identified as a cause of blepharitis [10].

Dry eye syndrome

As in the case of blepharitis, microbiological studies indicate that in patients with dry eye syndrome the number and bacteria diversity on the ocular surface is greater compared to healthy controls. This may be due to the abnormal composition of the tear film and its weaker antibacterial properties in patients with dry eye syndrome. Due to methodological limitations, studies do not agree on the type of bacteria prevalent in patients with dry eye syndrome. However, they point out to the role of *Staphylococcus* spp. or *Corynebacterium* spp. [11].

It should also be noted that an excessive number of bacteria on the ocular surface in patients with dry eye syndrome may not only result from the condition itself but may also exacerbate disease symptoms by affecting meibomian gland dysfunction.

Allergic conjunctivitis

More and more data indicate reduced ocular surface microbiome in patients with allergic conjunctivitis, particularly in its treatment-resistant form. These observations are consistent with the “hygiene hypothesis”, according to which decreased childhood exposure to pathogens, including bacteria, is associated with later development of allergies. However, it should be emphasized that it has not yet been established whether allergic conjunctivitis leads to alterations in the ocular surface microbiome. Nevertheless, numerous data indicate that the severity of symptoms in allergic conjunctivitis can be reduced by rebalancing the ocular surface microbiome [12].

Keratitis

Marginal keratitis is a classic example of a disease in which an imbalance of ocular surface microbiome (overexposure to bacterial antigens, including *Staphylococcus* spp.) is the di-

rect cause of eye disease. Marginal keratitis is not a direct bacterial infection of the cornea, but an interstitial hypersensitivity reaction to staphylococcal epitopes. Furthermore, many microbiological studies indicate that the ocular surface microbiome dysbiosis may be an important risk factor for bacterial or fungal keratitis [13, 14].

Endophthalmitis

Endophthalmitis is one of the most serious complications associated with intraocular surgery and intravitreal injections. *Staphylococcus epidermidis*, commonly found as a part of the normal ocular microbiota, is one of the most common causes (up to 70%) of postoperative endophthalmitis. In addition, reducing the ocular bacterial load with povidone-iodine solution is one of the main methods of preventing postoperative endophthalmitis after cataract surgery or intravitreal injections [15].

METHODS OF CONTROLLING THE OCULAR MICROBIOME

Numerous data indicating the role of ocular surface microbiome dysbiosis in the pathogenesis of ophthalmic diseases contributed to the search for effective methods of its regulation. Common treatment methods include topical and systemic antibiotic therapy, antiparasitic drugs, antiseptics, and eyelid margin hygiene.

Antibiotic therapy

Antibiotic therapy is the classic plan of combating excessive bacterial colonization in blepharitis, keratitis or in the prevention of endophthalmitis. Bacitracin and erythromycin are most commonly used for the treatment of blepharitis and marginal keratitis. Topical antibiotics are recommended twice daily for 2–8 weeks to reduce bacterial colonization of the eyelid margins. Oral antibiotics, including doxycycline or azithromycin, can be used in treatment-resistant cases. These substances are effective due to their antimicrobial and anti-inflammatory properties. A significant disadvantage of doxycycline is that it needs to be taken for 1–3 months at a dose of 20–200 mg/24 h, whereas the 3-day azithromycin treatment needs to be repeated several times with a daily dose of 500 mg. However, a Cochrane meta-analysis questioned the role of systemic antibiotics in the treatment of blepharitis since their use is associated with negative effects on the human physiological flora and the risk of side effects such as diarrhea and abdominal pain [16]. However, antibiotic therapy has been studied in excessive lid margin infestation with *Demodex* mites. The most common treatment of *Demodex* infestation is metronidazole cream or gel at a concentration of 0.75–2% applied 1–2 times daily for 12–24 weeks [17, 18]. Some authors suggest systemic use of metronidazole (e.g., 250 mg of metronidazole 3 times/24 h for 2 weeks or 500 mg twice/24 h for 10 days) [19]. The significance of using anti-

biotic eye drops has also been studied in the context of preventing endophthalmitis after cataract surgery or intravitreal injections. Previous studies, including the ESCRS study that recruited nearly 14,000 patients, as well as the study by Storey et al. that analyzed data from nearly 120,000 patients, showed that the use of antibiotic drops does not reduce the risk of endophthalmitis after cataract surgery or intravitreal injections [20, 21]. In addition, the widespread use of antibiotics for such indications may promote antibiotic resistance at the population level.

Antiparasitic drugs

Antiparasitic drugs are used for excessive *Demodex* infestation of lid margins. Ivermectin 1% cream is the most commonly prescribed antiparasitic for this indication [22]. Ivermectin is a broad-spectrum antiparasitic that blocks chloride channels in peripheral neurons leading to nerve paralysis and parasite death. It is worth mentioning that in 2015 William Campbell and Satoshi Ōmura were awarded the Nobel Prize in medicine for its discovery. Studies show that applying 1% ivermectin cream for 15 minutes once a week can reduce the number of nematodes and improve ocular symptoms in patients with blepharitis [22]. Similar results were observed after oral application. The study compared two different dosing regimens of ivermectin: 6 mg/twice daily on the first day of the study and after 2 weeks, or 200 µg/kg bw. on the first day of the study and after a week [23, 24].

Antiseptics

The ocular surface colonization can be also regulated with topical antiseptics that reduce the microbial count. Unlike antibiotics, antiseptics are not used orally. Their mechanism of action is nonspecific, which means that they may also damage human cells [25]. One of the most commonly used antiseptics in ophthalmology is povidone-iodine solution. Its mechanism of action damages bacterial cell membranes. The European Society of Cataract and Refractive Surgery recommends applying 5% povidone-iodide to the conjunctival sac for a duration of minimum 3 min prior to surgery. In addition, 5% povidone-iodide is commonly recommended to be administered at least 30 s prior to intravitreal injections [20]. If patients are allergic to povidone-iodide solution, it is recommended the use the solution of aqueous chlorhexidine (0.05% or 0.1%) [26]. Another antiseptic commonly used to reduce *Demodex* spp. infestation is tea tree oil, which contains, among other things, terpinen-4-ol. Different concentrations and methods of applying tea tree oil are employed in clinical practice. The antiparasitic mechanism of terpinen-4-ol against *Demodex* mites is unknown. However, 1% tea tree oil causes *Demodex* mites to migrate to the skin surface and facilitates their mechanical removal. Tea tree oil at higher concentrations (30% or 50%) is not only directly toxic to parasites, but also to human skin. Therefore, treatment with

higher concentrations should be carried out only in a doctor's office [10, 27]. It should also be noted that formulations containing pure terpinen-4-ol may cause fewer side effects than those based on the tea tree oil, although their efficacy (at the same concentration) remains the same [28].

Lid margin hygiene

Lid margin hygiene is the removal of exfoliated epidermis, secretions of glands located on the lid margins, as well as the microbiome located on the eyelashes and the lid margin. The most common method of lid margin hygiene involves warming the eyelid with a water compress or a specialized warming eye mask filled with, e.g., flaxseed (e.g., Blepha Eyebag, Thea, France), massaging the eyelid to remove blockage in meibomian glands, and cleaning the lid margins with wipes containing natural active ingredients, such as Blephaclean (Thea, France). Heat is a very important component of this treatment regimen, as it helps liquefy the meibomian glands contents, and significantly facilitate their removal after massage and wiping with specialized wipes. Frequency and duration of treatment depend on the severity of lesions, e.g., twice a day for 5 days or once a day for 30 days [29]. Lid margin hygiene is used to treat blepharitis, dry eye syndrome, marginal keratitis, and to prevent postoperative infections. Studies have shown that properly performed lid margin hygiene reduces the ocular surface microbiota in a clinically significant way [30]. The first line treatment for anterior blepharitis is lid margin hygiene. Dried secretions and bacterial colonies on the eyelashes cause ocular surface inflammation and patient discomfort. If dry eye syndrome results from meibomian gland dysfunction, eyelid margin hygiene can improve oil glands' function and reduce *Demodex* spp. population that is often responsible for the meibomian gland dysfunction [31]. Lid margin hygiene is also recommended

in allergic conjunctivitis because it helps reduce exposure to allergens on the eyelashes and the number of pro-inflammatory products of microbiome metabolism, such as short-chain fatty acids. Available data suggest that lid margin hygiene may also play an important role in preoperative microbiome reduction. Although there is a lack of clinical, prospective randomized trials demonstrating the role of lid margin hygiene in preventing intraocular inflammation, microbiological cross-sectional studies indicate that lid margin hygiene may significantly reduce the bacterial population on the ocular surface [30].

The role of lid margin hygiene in the context of increasing antibiotic resistance

In recent years, ocular surface microbiome has become increasingly resistant to antibiotics [32]. Therefore, reducing ocular surface microbiome without antibiotics is gaining in importance. For instance, lid margin hygiene and antiseptics can be employed. Taking into account the number of injections and cataract removal procedures, as well as the recommended duration of povidone iodide exposure prior to the ophthalmic procedures (30 s and 3 min, respectively), it should be considered whether a combination of lid margin hygiene and antiseptics may optimize the timing of procedures without increasing the risk of postoperative infection and antibiotic resistance.

Conclusions

Many ophthalmic diseases are potentially associated with qualitative and quantitative disruption of the ocular surface microbiota. There are different methods of its regulation. It should be noted that lid margin hygiene is the easiest method that does not lead to antibiotic resistance.

CORRESPONDENCE

assist. prof. Janusz Skrzypecki, MD, PhD

The Independent Public Clinical Ophthalmology Hospital
00-576 Warszawa, ul. Marszałkowska 24/26
e-mail: jskrzypecki@wum.edu.pl

ORCID

Janusz Skrzypecki – ID – <http://orcid.org/0000-0002-6054-163X>

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