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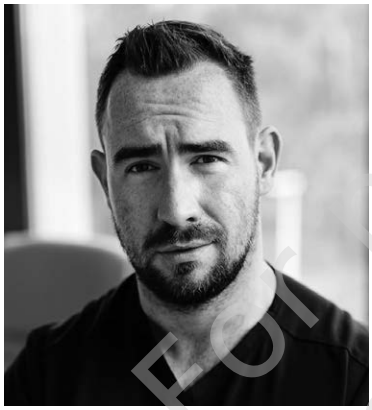
Management of ocular surface disorders according to the guidelines of the Tear Film & Ocular Surface Society Dry Eye Workshop (DEWSII) Report



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HIGHLIGHTS

Only modern approach to ocular surface disease, combining pharmacotherapy, neuromodulation, and advanced technologies, may give relieve from daily chronic pain.

ABSTRACT

Ocular surface disorders, including dry eye disease, affect 5–50% of the population, with prevalence increasing with age, especially among women. Symptoms such as dryness, burning, and eye fatigue significantly reduce quality of life. The tear film consists of aqueous-mucin and lipid fractions, providing protection and hydration for the eye. Meibomian gland dysfunction, which disrupts the lipid layer, accounts for most cases of dry eye disease by causing excessive tear evaporation. A modern approach to ocular surface disorder therapy, combining pharmacotherapy, neuromodulation, and advanced technologies, may relieve daily chronic eye pain.

Key words: ocular surface disease, dry eye, DEWS II, Meibomian gland disfunction

INTRODUCTION

According to the 2017 definition of the updated Dry Eye Workshop Report published by the Tear Film and Ocular Surface Society (DEWS II), ocular surface disease (DED, dry eye disease) is a multifactorial ocular surface disorder characterized by abnormal tear homeostasis and associated ocular discomfort caused by multiple etiologic factors, the most important of which are tear film instability and hyperosmolarity, inflammation and damage of the ocular surface, and neurosensory dysfunction [1].

According to Craig et al. [2], tears are classified as:

- Basal (occurring when the eyelids are open) – tears that cover the ocular surface; their deficiency is the main cause of ocular surface disorders due to insufficient production of the aqueous layer (ADDE, aqueous deficient dry eye).
- Reflex – their secretion is triggered by irritation of the ocular surface (e.g. fumes from cutting onions) or stimulation of the reflex arc.
- Emotional – secreted in response to emotions.
- Under the closed eyelid – tears that can be collected for analysis immediately after waking up.

Basal tears, reflex tears and emotional tears are produced by the lacrimal gland as a result of stimulation of the nerve arc, but they differ, for example, in the concentration of proteins [3]. During sleep, the secretion of the lacrimal gland is reduced, so there is a higher concentration of proteins (from serum) in the tear preparations collected immediately after waking up, which come from the blood vessels of the conjunctiva [2].

EPIDEMIOLOGY OF OCULAR SURFACE DISORDERS

One in seven patients between the ages of 65 and 84 report intermittent or chronic symptoms of DED [4]. According to some studies, signs resulting from ocular surface disorders affect 40 million patients worldwide each year and are among the main reasons for visits to ophthalmologists' offices [5]. Unfortunately, due to the multiplicity of diagnostic criteria and the ambiguity in the classification of ocular surface disorders, epidemiologic studies are very difficult to perform. Many studies have been published in the world literature; however, their methodologies are not systematized, and meta-analyses are also lacking. According to an updated report of the Dry Eye Workshop published by the Tear Film and Ocular Surface Society, the prevalence of DED ranges from 5% to 50% depending on the studied population, and the percentage increases with age [6]. In studies assessing the prevalence of clinical symptoms only, the percentage is higher, reaching as high as 75% in some populations (including Asian and Caucasian) and contact lens wearers [1]. The gender difference in the prevalence of DED also increases with age, being 1.33–1.74 times higher in women than in men [7–11]. A high incidence of DED has been reported in school-aged children, highlighting the need for future studies evaluating risk factors such as smartphone use. Population-based studies in the southern hemisphere have not been conducted in the last decade, making it impossible to properly assess socioeconomic and environmental risk factors [7–9, 12, 13].

STRUCTURE OF THE TEAR FILM

The ocular surface includes the cornea, the conjunctiva of the eyelid and eyeball, the goblet cells, the lacrimal glands and the accessory glands of the eyelid, and the Meibomian glands and eyelashes within them. These structures form a functional unit whose function is to produce the tear film, commonly known as tears [14].

Tear film covers the curvature of the cornea, serves to nourish and moisturize the eyeball, and participates in the transport of oxygen to the cornea. In addition, tears contain antimicrobial peptides, proteins and dissolved immunoglobulins that form a protective layer on the eyeball to protect it from microorganisms. DED is immunologically heterogeneous. Using modern proteomic methods, more than 2,000 proteins and more than 200 peptides have been identified in the tear film [15–17]. The proteins and peptides clear the ocular surface of dead corneal epithelial cells. The tear film provides an inert environment for the cornea. Due to the difference in refractive indices between air (1.0000) and the tear film (1.3369), the air-tear film interface is the primary refractive power in the human eye with a focusing power of approximately 42 D [18]. The average pH of tears is between 6.8 and 8.2, and gender has no effect on its value. The pH is dependent on age, time of day, eye closure, blinking and tearing [19-25].

According to the model proposed by Wolff et al. [26, 27], the tear film is composed of:

- The mucin layer composed of high molecular weight glycoproteins produced by the disc and sternal goblet cells. This fraction directly covers the epithelium lining the anterior surface of the cornea.
- The aqueous layer, which consists of the secretions of the main lacrimal glands and the Wolfring and Krause secondary lacrimal glands. This fraction is the largest volume component of the tear film.
- The lipid layer, produced by the Meibomian, Zeiss and Moll's glands.

According to the 2017 DEWS II report, there are 2 fractions of the tear film [1]:

- mucin-water fraction
- lipid fraction.

In terms of dynamics, these fractions behave as a coherent functional unit [28]. The thickness of the tear film covering the cornea, as measured by optical coherence tomography, is approximately 2.0–5.5 μm [29–33]. This value is consistent with the results of studies using interferometric techniques. The thickness of the tear film covering the conjunctiva has not been clearly measured [29, 34]. Physiological daily secretion is approximately 1.5–2 mL of tears with a volume of 8 (±3) μL [35, 36]. The fluid is released into the conjunctival sac and is drained during the blink reflex. Tears are drained into the nasal cavity through the lacrimal punctum, lacrimal ducts, lacrimal sac and nasolacrimal duct. Only 16% (±5%) of tears per minute are drained through the lacrimal ducts, with the remainder evaporating [36, 37]. Tear secretion is controlled by the parasympathetic nervous system. Protein and electrolyte secretion is regulated by the sympathetic nervous system [38].

Fractions of the tear film

The normal tear film is a non-Newtonian emulsion consisting of a mucin-water fraction and a lipid fraction.

Mucin-water fraction

Mucins are found not only on the surface of the eye, but also in other organs of the human body, including the lining of the respiratory epithelium or the epithelium lining the stomach. The mucin fraction consists of mucopolysaccharides produced by goblet cells and conjunctival and corneal epithelial cells. There are two groups of mucins based on their size: large gel-forming mucins (including MUC5AC) and small non-gel-forming soluble transmembrane mucins (including MUC1, MUC6, MUC4). Mucins are also classified according to their transmembrane and secretory forms. Their concentration decreases with distance from the epithelial cells. Mucins contain protein domains rich in serine and threonine and are glycosylated by attachment of O-glycans (glycan chains make up to 80% of the mass of mucins).

The main functions of this mucosal component are to minimize frictional forces and tightly fill intercellular spaces. Its gel-like consistency provides a barrier to pathogens. It is hydrophilic in nature, unlike the hydrophobic corneal epithelium. The aqueous component after a full blink (i.e., when both eyelids close tightly) divides into an upper and lower meniscus. It is composed of 95% lacrimal gland secretions, with the remaining 5% being secretions from the secondary lacrimal glands of Wolfring and Krause. This fraction consists mainly of water, electrolytes, and dissolved mucins and proteins. It carries nutrients, immune proteins and maintains the proper osmolarity of the tear film. It contains soluble immunoglobulins, sodium, potassium, chloride, calcium, magnesium, bicarbonate, glucose, lactate, amino acids and urea [39].

Mucin disorders cause both tear instability and ocular surface damage.

Lipid fraction

According to studies, the thickness of the lipid fraction ranges from 15 nm to 157 nm, with an average thickness of 42 nm [40]. The lipid layer reduces the surface tension of the tear film and is mainly produced by Meibomian glands. The thickness of the tear film is not uniform over the entire surface The lipid layer protects the pre-corneal tear film from excessive evaporation [41, 42]. The exact structure of the lipid layer of the tear film is not known. Hypothetically, it consists of surfactant molecules at the interface with the mucin-water fraction and lipophilic molecules at the interface with the air.

MEIBOMIAN GLAND DYSFUNCTION

The term Meibomian gland dysfunction (MGD) was first used by Korb and Henriquez in the early 1980s [43]. The term is used to describe all disorders of the Meibomian glands, including those with a proliferative basis or congenital lesions [44, 45]. MGD is one of the major (approximately 80%) causes of evaporative DED. As defined by the International Workshop on Meibomian Gland Dysfunction, 31 March 2011 [14, 46]:

"Meibomian gland dysfunction is a chronic obstruction of the meibomian gland orifices accompanied by quantitative and/or qualitative changes in glandular secretions. This dysfunction leads to tear film abnormalities, DED, lid margin inflammation and ocular surface disorders".

In most cases, MGD is bilateral and symmetrical. It is often associated with blepharitis. The symptoms of both conditions are clinically similar and often overlap [47].

In the DEWS II report, the prevalence of MGD in people over 40 years of age was estimated to be 38-68% [48]. Unstable tear film and excessive evaporation are the main causes of the disease [49]. In the early stages of the disease, the course of MGD is asymptomatic, but as the disease progresses, lid margin lesions or posterior blepharitis associated with MGD appear.

Modern therapies for ocular surface disorders are based on the administration of preparations composed of various chemicals, such as cellulose derivatives or hyaluronic acid. However, despite their good ocular surface moisturizing properties, small molecules such as trehalose, L-carnitine, erythritol are included in the preparations [50, 51]. The international literature provides information on their osmoprotective effect by regulating intracellular and extracellular osmolarity. Hyperosmolarity is one of the main causes of cell apoptosis and inflammation in ocular surface diseases [50, 52]. These substances are also characterized by cytoprotective effects [53].

Despite many years of effort, there is currently no gold standard for topical therapy of ocular surface disease, yet tear film replacement is the cornerstone of any therapeutic regimen. When lid margin hygiene and tear supplementation with lubricating drops are inadequate and in severe forms of ocular surface disease, topical anti-inflammatory treatment, including preservative-free corticosteroids or preparations containing immunomodulatory substances such as cyclosporine A, should be added to the therapy according to the recommendations of the DEWS II report [38, 54].

Cyclosporin A is a cyclic immunomodulatory polypeptide with immunosuppressive activity. It has been shown to be effective in preventing allograft rejection, including rejection of a transplanted corneal flap [55]. The drug also has anti-inflammatory effects by inhibiting cellular immune responses. In the first step of its action, cyclosporin A binds to cyclophilin, a cytoplasmic protein of T lymphocytes. In the next step, the complex formed by the combination of cyclosporin and cyclophilin binds to calcineurin (a key calcium-dependent enzyme with phosphatase properties), preventing it from activating the nuclear factor of activated T cells (NFAT) – a transcription factor that stimulates the transcription of interleukin 2 (IL-2). Dephosphorylation of NFAT causes its translocation to the nucleus and initiation of transcription of genes for selected cytokines. The action of cyclosporine leads to cellular apoptosis. Cyclosporine A reduces the secretion of lymphokines, including IL-2, IL-3, IL-4, IL-5, tumor necrosis factor α (TNF-α), interferon γ (INF-γ), and T-cell growth factor (TCGF). This drug blocks cellular and humoral immune responses and modifies inflammatory processes. Its action is reversible, it does not cause lymphocytotoxic effects and it does not lead to proliferative processes.

In DED, cyclosporine A prevents pathological apoptosis of the secretory epithelium by blocking nonspecific pores of the mitochondrial membrane responsible for a transient increase in their permeability to molecules causing increased production of the tear film. It is used as an anti-inflammatory and anti-apoptotic agent. In the anti-inflammatory treatment regimen of severe DES, it is recommended to use cyclosporine A for 6 months along with a 2-month course of glucocorticosteroid therapy and artificial tears. It should be noted that topical cyclosporine A is also used to prevent graft rejection in corneal transplant patients.

According to the TFOS DEWS II report guidelines, the following are recommended as first-line therapy for ocular surface disorders:

- patient education
- modification of environmental factors
- dietary modification
- elimination of harmful general and topical medications (including those containing preservatives)
- tear film replacement with preservative-free moisturizing drops
- eyelid margin hygiene.

Although significant progress has been made in recent years in understanding the pathomechanisms of DED and implementing new treatment options, tear film replacement is the foundation of any DED therapy. Unfortunately, the short time a drop of a given solution remains on the ocular surface after instillation remains a challenge [34, 56–58]. As the frequency of instillation increases, the percentage of patients who fully adhere to the clinician's recommendations (patient compliance) decreases. Hypothetically, an increase in the viscosity of artificial tears should be associated with an increase in the time the products remain on the ocular surface and thus a decrease in the frequency of application [59]. Most studies on ocular surface retention have been performed in an animal model, and their methodology required the use of γ-scintigraphy techniques combined with radioactive particle labeling or positron emission tomography [60, 61]. As mentioned above, the ongoing challenges in the treatment of ophthalmic diseases are the bioavailability of the drug after administration and its penetration into the structures of the eyeball. In the results of these studies, products with a low molecular weight hyaluronic acid molecule had a longer retention time on the ocular surface [62, 63].

According to the definition of DED presented by TFOS DEWS II, inflammatory and immunological processes are an integral part of the pathophysiology of ocular surface disease.

If the basic treatment is not sufficient, the following are added:

- thermotherapy and massage of the meibomian glands
- therapy with terpinen-4-ol preparations [64, 65] (if demodicosis is diagnosed)
- occlusion of the lacrimal puncta [66–69]
- use of ointment or humidifier (initially only at night)
- use of IPL (intense pulse light) laser treatment and red waves – Meibomian gland revitalization with lid margin photobiostimulation in isolated MGD and associated demodicosis [70–74]
- use of antibiotic drops [75]
- use of glucocorticosteroid drops [76]
- use of tear-stimulating drops
- use of drops with immunomodulatory effects (including cyclosporine A or LFA-1 and ICAM-1 antagonists, e.g. lifitegrast) [38, 77–99]
- use of general antibiotic therapy (macrolide or tetracycline antibiotics) [100, 101]
- Meibomian gland probing [102–109]
- LipiFlow system therapy [110–114].

One of the main mechanisms responsible for the development of ocular surface inflammation is the impairment of lacrimal gland function, which leads to a decrease in the secretion of lactoferrin, which has a natural anti-inflammatory function, the release of interleukins IL-1, IL-8 and TNF-α, and metalloproteinases (MMP), among others. An increase in the concentration of MMP leads to the degradation of cells of the basement membrane of the epithelium. In the therapeutic regimens of anti-inflammatory treatment in DES, cyclosporine A is the drug of choice for severe and moderate cases of ocular surface disease with sicca keratoconjunctivitis. Cyclosporin A was isolated from the fungus *Tolypocladium inflatum*. It was thought to have antifungal properties. This drug is a calcineurin inhibitor and has potent immunosuppressive properties in the mechanisms of inhibition of T lymphocytes and inhibition of apoptosis of conjunctival epithelial cells.
Historically, immunosuppressive effects have been observed in dogs with idiopathic keratoconjunctivitis sicca. In clinical studies, a significant reduction in the CD4+ cell count was observed in patients. Drops containing 0.05% cyclosporine A solution significantly reduced corneal fluorescein staining by approximately 46-50% and improved Schirmer's test scores over a 6-month observation period [115]. These parameters, as well as Ocular Surface Disease Index (OSDI) questionnaire scores, also improved over an additional 6 months of follow-up [115, 116]. A decrease in the expression of the HLA-DR receptor on the surface of conjunctival cells was also observed. The above results of the Daull study [115] are consistent with the results of the SICCANOVE study [117], which confirmed the good safety profile of cyclosporine A. The use of the drug does not cause significant systemic adverse effects and is well tolerated by patients [118, 119].

CONCLUSIONS

DED, the most common ocular surface disease, is a disease of civilization and affects everyone, regardless of gender or age. Therefore, every patient should undergo a thorough evaluation of the ocular surface and tears during a comprehensive ophthalmic examination. Non-invasive tests and questionnaires are particularly valuable. If the patient is diagnosed with symptoms suggestive of ocular surface disease, the diagnosis should be expanded according to the algorithms [120].

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References

1. Craig JP, Nichols KK, Akpek EK et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017; 15(3): 276-83.
2. Craig JP, Willcox MD, Argüeso P et al.; members of TFOS International Workshop on Contact Lens Discomfort. The TFOS International Workshop on Contact Lens Discomfort: report of the contact lens interactions with the tear film subcommittee. Invest Ophthalmol Vis Sci. 2013; 54(11): TFOS123-56.
3. Belmonte C, Nichols JJ, Cox SM et al. TFOS DEWS II pain and sensation report. Ocul Surf. 2017; 15(3): 404-37.
4. Javadi MA, Feizi S. Dry eye syndrome. J Ophthalmic Vis Res. 2011; 6(3): 192-8.
5. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007; 5(2): 93-107.
6. Stapleton F, Alves M, Bunya VY et al. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017; 15(3): 334-65.
7. Malet F, Le Goff M, Colin J et al. Dry eye disease in French elderly subjects: the Alienor Study. Acta Ophthalmol. 2014; 92(6): e429-36.

8. Ahn JM, Lee SH, Rim TH et al.; Epidemiologic Survey Committee of the Korean Ophthalmological Society. Prevalence of and risk factors associated with dry eye: the Korea National Health and Nutrition Examination Survey 2010-2011. Am J Ophthalmol. 2014; 158(6): 1205-14.e7.
9. Viso E, Rodriguez-Ares MT, Gude F. Prevalence of and associated factors for dry eye in a Spanish adult population (the Salnes Eye Study). Ophthalmic Epidemiol. 2009; 16(1): 15-21.
10. Tan LL, Morgan P, Cai ZQ et al. Prevalence of and risk factors for symptomatic dry eye disease in Singapore. Clin Exp Optom. 2015; 98(1): 45-53.
11. Hashemi H, Khabazkhoob M, Kheirkhah A et al. Prevalence of dry eye syndrome in an adult population. Clin Exp Ophthalmol. 2014; 42(3): 242-8.
12. Galor A, Feuer W, Lee DJ et al. Prevalence and risk factors of dry eye syndrome in a United States veterans affairs population. Am J Ophthalmol. 2011; 152(3): 377-84.e2.
13. Paulsen AJ, Cruickshanks KJ, Fischer ME et al. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol. 2014; 157(4): 799-806.
14. Ambroziak AM. Stanowisko Polskiej Grupy Ekspertów Akademii Powierzchni Oka. Wydanie pierwsze. Medical Education, Warszawa 2017.
15. Azkargorta M, Soria J, Ojeda C et al. Human Basal Tear Peptidome Characterization by CID, HCD, and ETD Followed by in Silico and in Vitro Analyses for Antimicrobial Peptide Identification. J Proteome Res. 2015; 14(6): 2649-58.
16. Zhou L, Beuerman RW. The power of tears: how tear proteomics research could revolutionize the clinic. Expert Rev Proteomics. 2017; 14(3): 189-91.
17. Zhou L, Zhao SZ, Koh SK et al. In-depth analysis of the human tear proteome. J Proteomics. 2012; 75(13): 3877-85.
18. Benjamin WJ, Borish IM. Borish's Clinical Refraction. Saunders, Philadelphia 1998: 2-29.
19. Altman PL, Dittmer DS. Man. Biology Data Book, in Physical properties and chemical composition of tears. Federation of American Societies of Experimental Biology, Maryland 1974: 2032-40.
20. Norn MS. Tear fluid pH in normals, contact lens wearers, and pathological cases. Acta Ophthalmol (Copenh). 1988; 66(5): 485-9.
21. Fischer FH, Wiederholt M. Human precorneal tear film pH measured by microelectrodes. Graefes Arch Clin Exp Ophthalmol. 1982; 218(3): 168-70.
22. McCarey BE, Wilson LA. pH, osmolarity and temperature effects on the water content of hydrogel contact lenses. Contact Intraocul Lens Med J. 1982; 8(3): 158-67.
23. Coles WH, Jaros PA. Dynamics of ocular surface pH. Br J Ophthalmol. 1984; 68(8): 549-52.
24. Andrés S, García ML, Espina M et al. Tear pH, air pollution, and contact lenses. Am J Optom Physiol Opt. 1988; 65(8): 627-31.
25. Janszky I, Vámosi P, Országh I et al. Demonstration of increasing standard pH value of lacrimal fluid with increase of flow rate. Acta Ophthalmol Scand. 2001; 79(2): 180-3.
26. Wolff E. The muco-cutaneous junction of the lid margin and the distribution of the tear fluid. Trans Ophthalmol Soc UK. 1946; 66: 291-308.
27. Holly FJ, Lemp MA. Tear physiology and dry eyes. Surv Ophthalmol. 1977; 22(2): 69-87.
28. Yokoi N, Bron A, Georgiev G. The precorneal tear film as a fluid shell: the effect of blinking and saccades on tear film distribution and dynamics. Ocul Surf. 2014; 12: 252-66.
29. Wozniak PA, Schmidl D, Bata AM et al. Effect of different lubricant eye gels on tear film thickness as measured with ultrahigh-resolution optical coherence tomography. Acta Ophthalmol. 2017; 95(4): e307-13.
30. Wang J, Fonn D, Simpson TL et al. Precorneal and pre- and postlens tear film thickness measured indirectly with optical coherence tomography. Invest Ophthalmol Vis Sci. 2003; 44(6): 2524-8.
31. Aranha Dos Santos V, Schmetterer L, Gröschl M et al. In vivo tear film thickness measurement and tear film dynamics visualization using spectral domain optical coherence tomography. Opt Express. 2015; 23(16): 21043-63.
32. Schmoll T, Unterhuber A, Kolbitsch C et al. Precise thickness measurements of Bowman's layer, epithelium, and tear film. Optom Vis Sci. 2012; 89(5): E795-802.
33. Werkmeister RM, Alex A, Kaya S et al. Measurement of tear film thickness using ultrahigh-resolution optical coherence tomography. Invest Ophthalmol Vis Sci. 2013; 54(8): 5578-83.
34. Chen Q, Wang J, Tao A et al. Ultrahigh-resolution measurement by optical coherence tomography of dynamic tear film changes on contact lenses. Invest Ophthalmol Vis Sci. 2010; 51(4): 1988-93.
35. Mishima S, Gasset A, Klyce SD Jr et al. Determination of tear volume and tear flow. Invest Ophthalmol. 1966; 5(3): 264-76.
36. Kuppens EV, Stolwijk TR, de Keizer RJ et al. Basal tear turnover and topical timolol in glaucoma patients and healthy controls by fluorophotometry. Invest Ophthalmol Vis Sci. 1992; 33(12): 3442-8.

37. van Best JA, Benitez del Castillo JM, Coulangeon LM. Measurement of basal tear turnover using a standardized protocol. European concerted action on ocular fluorometry. Graefes Arch Clin Exp Ophthalmol. 1995; 233(1): 1-7.
38. Bron AJ, de Paiva CS, Chauhan SK et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017; 15(3): 438-510.
39. Begley C, Simpson T, Liu H et al. Quantitative analysis of tear film fluorescence and discomfort during tear film instability and thinning. Invest Ophthalmol Vis Sci. 2013; 54(4): 2645-53.
40. King-Smith PE, Hinel EA, Nichols JJ. Application of a novel interferometric method to investigate the relation between lipid layer thickness and tear film thinning. Invest Ophthalmol Vis Sci. 2010; 51(5): 2418-23.
41. Peng C, Cerretani C, Li Y et al. Flow Evaporimeter To Assess Evaporative Resistance of Human Tear-Film Lipid Layer. Industrial & Engineering Chemistry Research, 2014; 53(47): 18130-9.
42. Knop E, Knop N, Millar T et al. 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.
43. Korb DR, Henriquez AS. Meibomian gland dysfunction and contact lens intolerance. J Am Optom Assoc. 1980; 51(3): 243-51.
44. Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. Classification and grading of lid changes. Eye (Lond). 1991; 5 (Pt 4): 395-411.
45. Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification, and grading. Ocul Surf. 2003; 1(3): 107-26.
46. Nelson JD, Shimazaki J, Benitez-del-Castillo JM 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.
47. Lindsley K, Matsumura S, Hatef E et al. Interventions for chronic blepharitis. Cochrane Database Syst Rev. 2012; 2012(5): CD005556.
48. Willcox MDP, Argüeso P, Georgiev GA et al. TFOS DEWS II Tear Film Report. Ocul Surf. 2017; 15(3): 366-403.
49. King-Smith PE, Nichols JJ, Nichols KK et al. Contributions of evaporation and other mechanisms to tear film thinning and break-up. Optom Vis Sci. 2008; 85(8): 623-30.
50. Baudouin C, Aragona P, Messmer EM et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013; 11(4): 246-58.
51. Snibson GR, Greaves JL, Soper ND et al. Ocular surface residence times of artificial tear solutions. Cornea. 1992; 11(4): 288-93.
52. Ambroziak AM, Langwińska-Wośko E, Korwin M. Osmolarność – aktualne spojrzenie na nowy standard w diagnostyce zaburzeń filmu łzowego. Kontaktologia i Optyka Okulistyczna. 2010; 1(25): 42-9.
53. Ambroziak AM, Nasiłowska-Paciorek A. Immunomodulacja miejscowa w przebiegu zespołu dysfunkcyjnych łez i schorzeń powierzchni oka – cyklosporyna. Okulistyka „Kompendium Okulistyki" Program Edukacyjny dla lekarzy praktyków. 2017; 1(37).
54. Jones L, Downie LE, Korb D et al. TFOS DEWS II Management and Therapy Report. Ocul Surf. 2017; 15(3): 575-628.
55. Price MO, Price FW Jr. Efficacy of topical cyclosporine 0.05% for prevention of cornea transplant rejection episodes. Ophthalmology. 2006; 113(10): 1785-90.
56. Paugh JR, Nguyen AL, Ketelson HA et al. Precorneal residence time of artificial tears measured in dry eye subjects. Optom Vis Sci. 2008; 85(8): 725-31.
57. Zhu H, Chauhan A. Effect of viscosity on tear drainage and ocular residence time. Optom Vis Sci. 2008; 85(8): 715-25.
58. Yellepeddi VK, Palakurthi S. Recent Advances in Topical Ocular Drug Delivery. J Ocul Pharmacol Ther. 2016; 32(2): 67-82.
59. Bandlitz S, Purslow C, Murphy PJ et al. Time course of changes in tear meniscus radius and blink rate after instillation of artificial tears. Invest Ophthalmol Vis Sci. 2014; 55(9): 5842-7.
60. Kuntner C, Wanek T, Hoffer M et al. Radiosynthesis and assessment of ocular pharmacokinetics of (124)I-labeled chitosan in rabbits using small-animal PET. Mol Imaging Biol. 2011; 13(2): 222-6.
61. Gupta H, Malik A, Khar RK et al. Physiologically active hydrogel (in situ gel) of sparfloxacin and its evaluation for ocular retention using gamma scintigraphy. J Pharm Bioallied Sci. 2015; 7(3): 195-200.
62. Wilson CG. Topical drug delivery in the eye. Exp Eye Res. 2004; 78(3): 737-43.
63. Snibson GR, Greaves JL, Soper ND et al. Precorneal residence times of sodium hyaluronate solutions studied by quantitative gamma scintigraphy. Eye (Lond). 1990; 4 (Pt 4): 594-602.
64. Cheung IMY, Xue AL, Kim A et al. In vitro anti-demodectic effects and terpinen-4-ol content of commercial eyelid cleansers. Cont Lens Anterior Eye. 2018; 41(6): 513-7.
65. Tighe S, Gao YY, Tseng SC. Terpinen-4-ol is the Most Active Ingredient of Tea Tree Oil to Kill Demodex Mites. Transl Vis Sci Technol. 2013; 2(7): 2.
66. Jehangir N, Bever G, Mahmood SM et al. Comprehensive Review of the Literature on Existing Punctal Plugs for the Management of Dry Eye Disease. J Ophthalmol. 2016; 2016: 9312340.
67. Song JS, Woo IH, Eom Y et al. Five Misconceptions Related to Punctal Plugs in Dry Eye Management. Cornea. 2018; 37(Suppl. 1): S58-S61.

68. Xie J, Wang C, Ning Q et al. A new strategy to sustained release of ocular drugs by one-step drug-loaded microcapsule manufacturing in hydrogel punctal plugs. Graefes Arch Clin Exp Ophthalmol. 2017; 255(11): 2173-84.
69. 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.
70. Arita R, Mizoguchi T, Fukuoka S et al. Multicenter Study of Intense Pulsed Light Therapy for Patients With Refractory Meibomian Gland Dysfunction. Cornea. 2018; 37(12): 1566-71.
71. Gupta PK, Vora GK, Matossian C et al. Outcomes of intense pulsed light therapy for treatment of evaporative dry eye disease. Can J Ophthalmol. 2016; 51(4): 249-53.
72. Vegunta S, Patel D, Shen JF. Combination Therapy of Intense Pulsed Light Therapy and Meibomian Gland Expression (IPL/MGX) Can Improve Dry Eye Symptoms and Meibomian Gland Function in Patients With Refractory Dry Eye: A Retrospective Analysis. Cornea. 2016; 35(3): 318-22.
73. Vora GK, Gupta PK. Intense pulsed light therapy for the treatment of evaporative dry eye disease. Curr Opin Ophthalmol. 2015; 26(4): 314-8.
74. Zhu B, Jin X. Multicenter Study of Intense Pulsed Light Therapy for Patients With Refractory Meibomian Gland Dysfunction. Cornea, 2019.
75. Mencucci R, Pellegrini-Giampietro DE, Paladini I et al. Azithromycin: assessment of intrinsic cytotoxic effects on corneal epithelial cell cultures. Clin Ophthalmol. 2013; 7: 965-71
76. Alves M, Fonseca EC, Alves MF et al. Dry eye disease treatment: a systematic review of published trials and a critical appraisal of therapeutic strategies. Ocul Surf. 2013; 11(3): 181-92.
77. Abidi A, Shukla P, Ahmad A. Lifitegrast: A novel drug for treatment of dry eye disease. J Pharmacol Pharmacother. 2016; 7(4): 194-8.
78. Donnenfeld ED, Karpecki PM, Majmudar PA et al. Safety of Lifitegrast Ophthalmic Solution 5.0% in Patients With Dry Eye Disease: A 1-Year, Multicenter, Randomized, Placebo-Controlled Study. Cornea. 2016; 35(6): 741-8.
79. Donnenfeld ED, Perry HD, Nattis AS et al. Lifitegrast for the treatment of dry eye disease in adults. Expert Opin Pharmacother. 2017; 18(14): 1517-24.
80. Godin MR, Gupta PK. Lifitegrast ophthalmic solution in the treatment of signs and symptoms of dry eye disease: design, development, and place in therapy. Clin Ophthalmol. 2017; 11: 951-7.
81. Guimaraes de Souza R, Yu Z, Stern ME et al. Suppression of Th1-Mediated Keratoconjunctivitis Sicca by Lifitegrast. J Ocul Pharmacol Ther. 2018; 34(7): 543-9.
82. Holland EJ, Luchs J, Karpecki PM et al. Lifitegrast for the Treatment of Dry Eye Disease: Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3). Ophthalmology. 2017; 124(1): 53-60.
83. Holland EJ, Whitley WO, Sall K et al. Lifitegrast clinical efficacy for treatment of signs and symptoms of dry eye disease across three randomized controlled trials. Curr Med Res Opin. 2016; 32(10): 1759-65.
84. Hussar DA, Cheeseman RS 2nd. Lifitegrast, Bezlotoxumab, and Sugammadex sodium. J Am Pharm Assoc (2003). 2017; 57(2): 284-7.
85. Keating GM. Lifitegrast Ophthalmic Solution 5%: A Review in Dry Eye Disease. Drugs. 2017; 77(2): 201-8.
86. Lollett IV, Galor A. Dry eye syndrome: developments and lifitegrast in perspective. Clin Ophthalmol. 2018; 12: 125-39.
87. Nichols KK, Donnenfeld ED, Karpecki PM et al. Safety and tolerability of lifitegrast ophthalmic solution 5.0%: Pooled analysis of five randomized controlled trials in dry eye disease. Eur J Ophthalmol. 2019; 29(4): 394-401.
88. Nichols KK, Holland E, Toyos MM et al. Ocular comfort assessment of lifitegrast ophthalmic solution 5.0% in OPUS-3, a Phase III randomized controlled trial. Clin Ophthalmol. 2018; 12: 263-70.
89. Patel J, Franko J. Lifitegrast Ophthalmic Solution 5% (Xiidra) for Dry Eye Disease. Am Fam Physician. 2018; 98(2): 119-20.
90. Paton DM. Lifitegrast: First LFA-1/ICAM-1 antagonist for treatment of dry eye disease. Drugs Today (Barc). 2016; 52(9): 485-93.
91. Perez VL, Pflugfelder SC, Zhang S et al. Lifitegrast, a Novel Integrin Antagonist for Treatment of Dry Eye Disease. Ocul Surf. 2016; 14(2): 207-15.
92. Semba CP, Gadek TR. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. Clin Ophthalmol. 2016; 10: 1083-94.
93. Sheppard JD, Torkildsen GL, Lonsdale JD et al.; OPUS-1 Study Group. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. Ophthalmology. 2014; 121(2): 475-83.
94. Skoczeń S, Balwierz W, Moryl-Bujakowska A et al.; Polish Pediatric Leukemia/Lymphoma Study Group. Ostra białaczka limfoblastyczna u dzieci ze wstepną leukocytozą powyżej 50,000/mm3: podsumowanie wyników leczenia Polskiej Pediatrycznej Grupy ds. Leczenia Białaczek i Chłoniaków. Przegl Lek. 2006; 63(1): 11-4.
95. Sobolewski B, Doman P, Stetkiewicz T et al. The toxic impact of local anaesthetics in menopausal women: causes, prevention and treatment after local anaesthetic overdose. Local anaesthetic systemic toxicity syndrome. Prz Menopauzalny. 2015; 14(1): 65-70.

96. Sun Y, Zhang R, Gadek TR et al. Corneal inflammation is inhibited by the LFA-1 antagonist, lifitegrast (SAR 1118). J Ocul Pharmacol Ther. 2013; 29(4): 395-402.
97. Tauber J, Karpecki P, Latkany R et al.; OPUS-2 Investigators. Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study. Ophthalmology. 2015; 122(12): 2423-31.
98. Wan KH, Chen LJ, Young AL. Efficacy and Safety of Topical 0.05% Cyclosporine Eye Drops in the Treatment of Dry Eye Syndrome: A Systematic Review and Meta-analysis. Ocul Surf. 2015; 13(3): 213-25.
99. Wurtele ES, Chappell J, Jones AD et al. Medicinal plants: a public resource for metabolomics and hypothesis development. Metabolites. 2012; 2(4): 1031-59.
100. Stone DU, Chodosh J. Oral tetracyclines for ocular rosacea: an evidence-based review of the literature. Cornea. 2004; 23(1): 106-9.
101. Voils SA, Evans ME, Lane MT et al. Use of macrolides and tetracyclines for chronic inflammatory diseases. Ann Pharmacother. 2005; 39(1): 86-94.
102. Incekalan TK, Harbiyeli II, Yagmur M et al. Effectiveness of Intraductal Meibomian Gland Probing in Addition to the Conventional Treatment in Patients with Obstructive Meibomian Gland Dysfunction. Ocul Immunol Inflamm. 2019; 27(8): 1345-51.
103. Ma X, Lu Y. Efficacy of Intraductal Meibomian Gland Probing on Tear Function in Patients With Obstructive Meibomian Gland Dysfunction. Cornea. 2016; 35(6): 725-30.
104. Maskin SL. Intraductal meibomian gland probing relieves symptoms of obstructive meibomian gland dysfunction. Cornea. 2010; 29(10): 1145-52.
105. Maskin SL, Testa WR. Growth of meibomian gland tissue after intraductal meibomian gland probing in patients with obstructive meibomian gland dysfunction. Br J Ophthalmol. 2018; 102(1): 59-68.
106. Nakayama N, Kawashima M, Kaido M et al. Analysis of Meibum Before and After Intraductal Meibomian Gland Probing in Eyes With Obstructive Meibomian Gland Dysfunction. Cornea. 2015; 34(10): 1206-8.
107. Sik Sarman Z, Cucen B, Yuksel N et al. Effectiveness of Intraductal Meibomian Gland Probing for Obstructive Meibomian Gland Dysfunction. Cornea. 2016; 35(6): 721-4.
108. Syed ZA, Sutula FC. Dynamic Intraductal Meibomian Probing: A Modified Approach to the Treatment of Obstructive Meibomian Gland Dysfunction. Ophthalmic Plast Reconstr Surg. 2017; 33(4): 307-9.
109. Wladis EJ. Intraductal meibomian gland probing in the management of ocular rosacea. Ophthalmic Plast Reconstr Surg, 2012. 28(6): 416-8.
110. Finis D, Hayajneh J, König C et al. Evaluation of an automated thermodynamic treatment (LipiFlow®) system for meibomian gland dysfunction: a prospective, randomized, observer-masked trial. Ocul Surf. 2014; 12(2): 146-54.
111. Greiner JV. A single LipiFlow(R) Thermal Pulsation System treatment improves meibomian gland function and reduces dry eye symptoms for 9 months. Curr Eye Res. 2012; 37(4): 272-8.
112. Korb DR, Blackie CA. Case report: a successful LipiFlow treatment of a single case of meibomian gland dysfunction and dropout. Eye Contact Lens. 2013; 39(3): e1-3.
113. Lane SS, DuBiner HB, Epstein RJ et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. Cornea. 2012; 31(4): 396-404.
114. Zhao Y, Veerappan A, Yeo S et al.; Collaborative Research Initiative for Meibomian gland dysfunction (CORIM). Clinical Trial of Thermal Pulsation (LipiFlow) in Meibomian Gland Dysfunction With Preteatment Meibography. Eye Contact Lens. 2016; 42(6): 339-46.
115. Daull P, Lallemand F, Garrigue JS. Benefits of cetalkonium chloride cationic oil-in-water nanoemulsions for topical ophthalmic drug delivery. J Pharm Pharmacol. 2014; 66(4): 531-41.
116. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. Ophthalmology. 2007; 114(1): 76-9.
117. Baudouin C, Figueiredo FC, Messmer EM et al. A randomized study of the efficacy and safety of 0.1% cyclosporine A cationic emulsion in treatment of moderate to severe dry eye. Eur J Ophthalmol. 2017; 27(5): 520-30.
118. Leonardi A, Van Setten G, Amrane M et al. Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial. Eur J Ophthalmol. 2016; 26(4): 287-96.
119. Baudouin C, de la Maza MS, Amrane M et al. One-Year Efficacy and Safety of 0.1% Cyclosporine a Cationic Emulsion in the Treatment of Severe Dry Eye Disease. Eur J Ophthalmol. 2017; 27(6): 678-85.
120. Feder RS, Olsen TW, Prum BE Jr et al. Comprehensive Adult Medical Eye Evaluation Preferred Practice Pattern(®) Guidelines. Ophthalmology. 2016; 123(1): P209-36.

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