

CHAPTER 2

COMPREHENSIVE MANAGEMENT OF DRY EYE DISEASE: FROM CONVENTIONAL APPROACHES TO ADVANCED THERAPIES

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INTRODUCTION

Dry eye disease (DED) is a multifactorial disorder of the ocular surface that arises from disruption of tear film stability and results in ocular discomfort, fluctuating vision, and tissue damage (1). It represents one of the most common and challenging conditions encountered in ophthalmic practice (2). The pathophysiology of DED is complex, involving tear film instability, hyperosmolarity, inflammation, neurosensory abnormalities, and meibomian gland dysfunction, often in overlapping patterns (3).

Because of its chronic and recurrent nature, DED can substantially impair quality of life by interfering with common daily activities including reading, driving, and prolonged screen exposure (2). Advances in understanding the underlying pathophysiology have led to the development of a wide range of diagnostic tools and therapeutic approaches. Management strategies now range from patient education and lifestyle modifications to advanced pharmacological, biological, and surgical interventions (4).

This chapter provides a comprehensive overview of current treatment modalities for dry eye disease, highlighting both conventional approaches and recent innovations, and offering practical insights into their clinical application.

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Salivary gland transplantation

Submandibular or minor salivary glands can be transplanted to provide continuous lubrication in end-stage, severe aqueous-deficient DED unresponsive to other treatments, though complications limit us (89).

STEPWISE MANAGEMENT

Beyond individual therapies, a staged approach to management is widely recommended, in which treatment intensity is adjusted according to disease severity and patient response. This framework integrates options ranging from lifestyle modifications to advanced surgical procedures. Initial steps include patient education, environmental and dietary adjustments, and preservative-free artificial tears, preferably with lipid supplementation when meibomian gland dysfunction is present. Lid hygiene and warm compresses provide additional support. If symptoms persist, escalation may involve frequent use of lubricants, tear-conservation methods such as punctal occlusion or moisture devices, and in-office treatments for meibomian gland disease. Pharmacologic therapies can be introduced at this stage, including short courses of corticosteroids, long-term immunomodulators such as cyclosporine or lifitegrast, and selected topical or oral antibiotics. In more advanced disease, systemic secretagogues, serum-derived eye drops, or therapeutic contact lenses may be used. For severe or refractory cases, invasive options such as amniotic membrane grafting, tarsorrhaphy, or conjunctival reconstruction may be required (4).

CONCLUSION

Although a broad spectrum of treatments is available, optimal outcomes depend on matching the right therapy to the right patient. Initial measures often involve environmental and lifestyle adjustments, progressing to pharmacological or surgical interventions when necessary. Future research should prioritize the development of therapies.

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf.* 2017;15(3):276–283.
2. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II Epidemiology Report. *Ocul Surf.* 2017;15(3):334–365.
3. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. *Ocul Surf.* 2017;15(3):438–510.
4. L. Jones, L.E. Downie, D. Korb, J.M. Benitez-del-Castillo, R. Dana, S.X. Deng, et al. TFOS DEWS II management and therapy report. *Ocul Surf.* 15 (2017), pp. 575–628.

5. Markoulli M, Ahmad S, Arcot J, et al. TFOS Lifestyle: Impact of nutrition on the ocular surface. *Ocul Surf.* Jul 2023;29:226-271.
6. Moon J, Yoon CH, Choi SH, Kim MK. Can Gut Microbiota Affect Dry Eye Syndrome? *Int J Mol Sci.* Nov 10 2020;21(22).
7. Watane A, Raolji S, Cavuoto K, Galor A. Microbiome and immune-mediated dry eye: a review. *BMJ Open Ophthalmol.* Jun 2022;7(1).
8. Goodman CF, Doan T, Mehra D, et al. Case-Control Study Examining the Composition of the Gut Microbiome in Individuals With and Without Immune-Mediated Dry Eye. *Cornea.* Nov 1 2023;42(11):1340-1348.
9. Napolitano P, Filippelli M, Davinelli S, Bartollino S, dell'Omo R, Costagliola C. Influence of gut microbiota on eye diseases: an overview. *Ann Med.* Dec 2021;53(1):750-761.
10. Labetoulle M, Baudouin C, Benitez del Castillo JM, et al. How gut microbiota may impact ocular surface homeostasis and related disorders. *Progress in retinal and eye research.* 2024/05/01/ 2024;100:101250.
11. Askari G, Rafie N, Miraghajani M, Heidari Z, Arab A. Association between vitamin D and dry eye disease: A systematic review and meta-analysis of observational studies. *Cont Lens Anterior Eye.* Oct 2020;43(5):418-425.
12. Lane SS, DuBiner HB, Epstein RJ, Ernest PH, Greiner JV, Hardten DR, et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. *Cornea* 2012;31(4):396-404.
13. Goldberg DJ. Current trends in intense pulsed light. *J Clin Aesthet Dermatol* 2012;5(6):45-53.
14. Craig JP, Chen YH, Turnbull PR. Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci* 2015;56(3):1965-70.
15. Wegener AR, Meyer LM, Sch€onfeld CL. Effect of viscous agents on corneal density in dry eye disease. *J Ocul Pharmacol Ther* 2015;31(8):504-8.
16. Yu F, Liu X, Zhong Y, Guo X, Li M, Mao Z, et al. Sodium hyaluronate decreases ocular surface toxicity induced by benzalkonium chloride-preserved latanoprost: an in vivo study. *Invest Ophthalmol Vis Sci* 2013;54:3385-93.
17. Stapleton, F., Argüeso, P., Asbell, P., et al. (2025). TFOS DEWS III Digest Report. *American Journal of Ophthalmology.* Jun 3. Epub 2025.
18. Nasser L, Rozycka M, Gomez Rendon G, Navas A. Real-life results of switching from preserved to preservative-free artificial tears containing hyaluronate in patients with dry eye disease. *Clin Ophthalmol.* 2018;12:1519-1525.
19. Pinheiro R, Panfil C, Schrage N, Dutescu RM. The impact of glaucoma medications on corneal wound healing. *J Glaucoma* 2016;25(1):122-7.
20. Chen W, Zhang Z, Hu J, Xie H, Pan J, Dong N, et al. Changes in rabbit corneal innervation induced by the topical application of benzalkonium chloride. *Cornea* 2013;32(12):1599-606.
21. Lin Z, He H, Zhou T, Liu X, Wang Y, He H, et al. A mouse model of limbal stem cell deficiency induced by topical medication with the preservative benzalkonium chloride. *Invest Ophthalmol Vis Sci* 2013;54(9):6314-25.
22. Kim EC, Choi JS, Joo CK. A comparison of vitamin a and cyclosporine a 0.05% eye drops for treatment of dry eye syndrome. *Am J Ophthalmol* 2009;147(2): 206-13. e3.
23. Brzheskiy VV, Efimova EL, Vorontsova TN, Alekseev VN, Gusarevich OG, Shaidurova KN, et al. Results of a multicenter, randomized, double-masked, placebo-controlled clinical study of the efficacy and safety of Visomitin eye drops in patients with dry eye syndrome. *Adv Ther* 2015;32(12):1263-79.
24. Green K, MacKeen DL, Slagle T, Cheeks L. Tear potassium contributes to maintenance of corneal thickness. *Ophthalmic Res* 1992;24(2):99-102.
25. Smolin G, Foster CS, Azar DT, Dohlman CH. Smolin and Thoft's *The Cornea: Scientific Foundations and Clinical Practice*. 4th Lippincott Williams & Wilkins ed. Lippincott Williams & Wilkins; 2005.
26. Ubels JL, McCartney MD, Lantz WK, Beaird J, Dayalan A, Edelhauser HF. Effects of preservative-free artificial tear solutions on corneal epithelial structure and function. *Arch Ophthalmol* 1995;113(3):371-8.

27. Craig JP, Tomlinson A. Importance of the lipid layer in human tear film stability and evaporation. *Optom Vis Sci* 1997;74(1):8-13.
28. Lee SY, Tong L. Lipid-containing lubricants for dry eye: a systematic review. *Optom Vis Sci* 2012;89(11):1654-61.
29. Rieger G. Lipid-containing eye drops: a step closer to natural tears. *Ophthalmologica* 1990;201(4):206-12.
30. Shine WE, McCulley JP. Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality. *Arch Ophthalmol* 1998;116(7):849-52.
31. Geerling G, Daniels JT, Dart JK, Cree IA, Khaw PT. Toxicity of natural tear substitutes in a fully defined culture model of human corneal epithelial cells. *Invest Ophthalmol Vis Sci* 2001;42:948-56.
32. Freire V, Andollo N, Etxebarria J, Hernaez-Moya R, Duran JA, Morales MC. Corneal wound healing promoted by 3 blood derivatives: an in vitro and in vivo comparative study. *Cornea* 2014;33(6):614-20.
33. Akyol-Salman I. Effects of autologous serum eye drops on corneal wound healing after superficial keratectomy in rabbits. *Cornea* 2006;25(10):1178-81.
34. Hartwig D, Harloff S, Liu L, Schlenke P, Wedel T, Geerling G. Epitheliotropic capacity of a growth factor preparation produced from platelet concentrates on corneal epithelial cells: a potential agent for the treatment of ocular surface defects? *Transfusion* 2004;44(12):1724-31.
35. Hartwig D, Herminghaus P, Wedel T, Liu L, Schlenke P, Dibbelt L, et al. Topical treatment of ocular surface defects: comparison of the epitheliotropic capacity of fresh frozen plasma and serum on corneal epithelial cells in an in vitro cell culture model. *Transfus Med* 2005;15(2):107-13.
36. Semeraro F, Forbice E, Braga O, Bova A, Di Salvatore A, Azzolini C. Evaluation of the efficacy of 50% autologous serum eye drops in different ocular surface pathologies. *Biomed Res Int* 2014;2014:826970.
37. Hondur AM, Akcam HT, Karaca EE, Yazici Eroglu H, Aydin B. Autologous serum eye drops accelerate epithelial healing after LASEK. *Curr Eye Res* 2016;41(1):15-9.
38. Sagara H, Iida T, Saito K, Noji H, Ogasawara M, Oyamada H. Conservative treatment for late-onset bleb leaks after trabeculectomy with mitomycin C in patients with ocular surface disease. *Clin Ophthalmol* 2012;6:1273-9.
39. Ziakas NG, Boboridis KG, Terzidou C, Naoumidi TL, Mikropoulos D, Georgiadou EN, et al. Long-term follow up of autologous serum treatment for recurrent corneal erosions. *Clin Exp Ophthalmol* 2010;38(7):683-7.
40. Watson SL, Secker GA, Daniels JT. The effect of therapeutic human serum drops on corneal stromal wound-healing activity. *Curr Eye Res* 2008;33(8):641-52.
41. Harloff S, Hartwig D, Kasper K, Wedel T, Muller M, Geerling G. Epitheliotropic capacity of serum eye drops from healthy donors versus serum from immunosuppressed patients with rheumatoid arthritis. *Klin Monbl Augenheilkd* 2008;225:200-6.
42. Chiang CC, Lin JM, Chen WL, Tsai YY. Allogeneic serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. *Cornea* 2007;26(7):861-3.
43. Harritshøj LH, Nielsen C, Ullum H, Hansen MB, Julian HO. Ready-made allogeneic ABO-specific serum eye drops: production from regular male blood donors, clinical routine, safety and efficacy. *Acta Ophthalmol* 2014;92(8):783-6.
44. Yoon KC, Im SK, Park YG, Jung YD, Yang SY, Choi J. Application of umbilical cord serum eyedrops for the treatment of dry eye syndrome. *Cornea* 2006;25(3):268-72.
45. Yoon KC, Heo H, Im SK, You IC, Kim YH, Park YG. Comparison of autologous serum and umbilical cord serum eye drops for dry eye syndrome. *Am J Ophthalmol* 2007;144(1):86-92.
46. Ichikawa Y, Tokunaga M, Shimizu H, Moriuchi J, Takaya M, Arimori S. Clinical trial of ambroxol (Mucosolvan) in Sjögren's syndrome. *Tokai J Exp Clin Med* 1988;13(3):165-9.
47. Pokupeć R, Petricek I, Sikic J, Bradic M, Popovic-Suic S, Petricek G. Comparison of local acetylcysteine and artificial tears in the management of dry eye syndrome. *Acta Med Croat*

2005;59:337-40.

48. Albietz J, Sanfilippo P, Troutbeck R, Lenton LM. Management of filamentary keratitis associated with aqueous-deficient dry eye. *Optom Vis Sci* 2003;80(6):420-30.
49. Li M, Wang J, Shen M, Cui L, Tao A, Chen Z, et al. Effect of punctal occlusion on tear menisci in symptomatic contact lens wearers. *Cornea* 2012;31(9):1014-22.
50. Alfawaz AM, Algehedan S, Jastaneiah SS, Al-Mansouri S, Mousa A, Al-Assiri A. Efficacy of punctal occlusion in management of dry eyes after laser in situ keratomileusis for myopia. *Curr Eye Res* 2014;39(3):257-62.
51. Yaguchi S, Ogawa Y, Kamoi M, Uchino M, Tatematsu Y, Ban Y, et al. Surgical management of lacrimal punctal cauterization in chronic GVHD-related dry eye with recurrent punctal plug extrusion. *Bone Marrow Transpl* 2012;47(11):1465-9.
52. Sabti S, Halter JP, Braun Fr€ankl BC, Goldblum D. Punctal occlusion is safe and efficient for the treatment of keratoconjunctivitis sicca in patients with ocular GvHD. *Bone Marrow Transpl* 2012;47(7):981-4.
53. Kimura K, Yokoi N, Inagaki K, Komuro A, Sonomura Y, Kato H, et al. Treatment progress of large-size puncta and clinical investigation of the extrusion rate and other complications associated with large-size punctal plugs. *Nippon Ganka Gakkai Zasshi* 2014;118:490-4.
54. Sonomura Y, Yokoi N, Komuro A, Inagaki K, Kinoshita S. Clinical investigation of the extrusion rate and other complications of the SuperEagle plug. *Nippon Ganka Gakkai Zasshi* 2013;117:126-31.
55. Rumelt S, Remulla H, Rubin PA. Silicone punctal plug migration resulting in dacryocystitis and canaliculitis. *Cornea* 1997;16(3):377-9.
56. Bourkiza R, Lee V. A review of the complications of lacrimal occlusion with punctal and canalicular plugs. *Orbit* 2012;31(2):86-93.
57. Dohlman CH. Punctal occlusion in keratoconjunctivitis sicca. *Ophthalmology* 1978;85(12):1277-81.
58. Yazici B, Bilge AD, Naqadan F. Lacrimal Punctal Occlusion With Conjunctival Flap. *Ophthal Plast Reconstr Surg* 2015 Jul-Aug;31(4):300-2.
59. Panagopoulos A, Chalioulas K, Ramsay AS. 'Punctal switch' grafting for the treatment of dry eyes: our experience. *Ophthalmic Res* 2011;46(4):218-20.
60. Obata H, Ibaraki N, Tsuru T. A technique for preventing spontaneous loss of lacrimal punctal plugs. *Am J Ophthalmol* 2006;141(3):567-9.
61. Putterman AM. Canaliculectomy in the treatment of keratitis sicca. *Ophthalmic Surg* 1991;22(8):478-80.
62. Hyden D, Arlinger S. On the sneeze-reflex and its control. *Rhinology* 2007;45(3):218-9.
63. Baroody FM. How nasal function influences the eyes, ears, sinuses, and lungs. *Proc Am Thorac Soc* 2011;8(1):53-61.
64. Craig JP, Cohn G, Corbett D, Tenen A, Coroneo M, McAlister J, et al. Evaluating the Safety and Efficacy of Intranasal Neurostimulation for Dry Eye Disease: A Double-masked, Randomized, Controlled, Multicenter Study. *Optom Vis Sci* 2016;94:160041. E-abstract.
65. 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.
66. 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.
67. Lekhanont K, Leyngold IM, Suwan-Apichon O, Rangsin R, Chuck RS. Comparison of topical dry eye medications for the treatment of keratoconjunctivitis sicca in a botulinum toxin B-induced mouse model. *Cornea* 2007;26(1):84-9.
68. Shafiee A, Bucolo C, Budzynski E, Ward KW, Lopez FJ. In vivo ocular efficacy profile of mapracorat, a novel selective glucocorticoid receptor agonist, in rabbit models of ocular disease. *Invest Ophthalmol Vis Sci* 2011;52(3):1422-30.

69. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome. *Ophthalmology* 1999;106(4):811-6.
70. Sainz De La Maza Serra M, Simon Castellvi C, Kabbani O. Nonpreserved topical steroids and lacrimal punctal occlusion for severe keratoconjunctivitis sicca. *Arch Soc Esp Oftalmol* 2000;75:751-6.
71. Pinto-Fraga Jose, Lopez-Miguel Alberto, Gonzalez-García María J, Fernandez Itziar, Lopez-de-la-Rosa Alberto, Enriquez-de-Salamanca Amalia, et al. Topical Fluorometholone Protects the Ocular Surface of Dry Eye Patients from Desiccating Stress. *Ophthalmology* 2016;123(1):141-53.
72. Hong S, Kim T, Chung SH, Kim EK, Seo KY. Recurrence after topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren's syndrome. *J Ocul Pharmacol Ther* 2007;23(1):78-82.
73. Mataftsi A, Narang A, Moore W, Nischal KK. Do reducing regimens of fluorometholone for paediatric ocular surface disease cause glaucoma? *Br J Ophthalmol* 2011;95(11):1531-3.
74. Bilgihan K, Gürel G, Akata F, Hasanreisoglu B. Fluorometholone-induced cataract after photorefractive keratectomy. *Ophthalmologica* 1997;211(6):394-6.
75. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. *Immunopharmacology* 2000;47(2e3):119-25.
76. Gao J, Sana R, Calder V, Calonge M, Lee W, Wheeler LA, et al. Mitochondrial permeability transition pore in inflammatory apoptosis of human conjunctival epithelial cells and T cells: effect of cyclosporin A. *Invest Ophthalmol Vis Sci* 2013;54:4717-33.
77. Tsubota K, Fujita H, Tadano K, Takeuchi T, Murakami T, Saito I, et al. Improvement of lacrimal function by topical application of CyA in murine models of Sjogren's syndrome. *Invest Ophthalmol Vis Sci* 2001;42(1):101-10.
78. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *CsA Phase 3 Study Group. Ophthalmology* 2000;107(4):631-9.
79. Pflugfelder SC, De Paiva CS, Villarreal AL, Stern ME. Effects of sequential artificial tear and cyclosporine emulsion therapy on conjunctival goblet cell density and transforming growth factor-beta2 production. *Cornea* 2008;27(1):64-9.
80. Brignole F, Pisella PJ, Goldschild M, De Saint Jean M, Goguel A, Baudouin C. Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes. *Invest Ophthalmol Vis Sci* 2000;41(6):1356-63.
81. Strong B, Farley W, Stern ME, Pflugfelder SC. Topical cyclosporine inhibits conjunctival epithelial apoptosis in experimental murine keratoconjunctivitis sicca. *Cornea* 2005;24(1):80-5.
82. Gao J, Gelber-Schwalb TA, Addeo JV, Stern ME. Apoptosis in the lacrimal gland and conjunctiva of dry eye dogs. *Adv Exp Med Biol* 1998;438:453-60.
83. 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.
84. 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.
85. 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.
86. 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.
87. Hamill MB. Corneal injury. In: Krachmer JH, Mannis MJ, Holland EJ, editors. *Cornea*. Vol. 2. St. Louis: Mosby; 1997. pp. 1403-22
88. Mead, O. G., Tighe, S., & Tseng, S. C. G. Amniotic membrane transplantation for managing dry eye and neurotrophic keratitis. *Taiwan journal of ophthalmology* 2020, 10(1), 13-21.
89. Singh S, Basu S, Geerling G. Salivary gland transplantation for dry eye disease: Indications, techniques, and outcomes. *Ocul Surf.* 2022 Oct; 26:53-62.