

DEWS Management and Therapy

Management and Therapy of Dry Eye Disease: Report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT The members of the Management and Therapy Subcommittee assessed current dry eye therapies. Each member wrote a succinct evidence-based review on an assigned aspect of the topic, and the final report was written after review by and with consensus of all subcommittee members and the entire Dry Eye WorkShop membership. In addition to its own review of the literature, the Subcommittee reviewed the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force (ITF) Delphi Panel on Dry Eye. The Subcommittee favored the approach taken by the ITF, whose recommended treatments were based on level of disease severity. The recommendations of the Subcommittee are based on a modification of the ITF severity grading scheme, and suggested treatments were chosen from a menu of therapies for which evidence of therapeutic effect had been presented.

KEYWORDS DEWS, dry eye disease, Dry Eye WorkShop, management, therapy

Accepted for publication January 2007.

Management and Therapy Subcommittee members: **Stephen C. Pflugfelder, MD (Chair)**; Gerd Geerling, MD; Shigero Kinoshita, MD; Michael A. Lemp, MD; James McCulley, MD; Daniel Nelson, MD; Gary N. Novack, PhD; Jun Shimazaki, MD; Clive Wilson, PhD.

Proprietary interests of Subcommittee members are disclosed on pages 202 and 204.

Reprints are not available. Articles can be accessed at: www.tearfilm.org.

Correspondence in regard to this chapter should be addressed to Stephen C. Pflugfelder MD, Ophthalmology-Ocular Surf Ctr, Cullen Eye Institute, 6565 Fannin Street NC 205, Houston, TX 77030. Tel: 713-798-4732. Fax: 713-798-1457. Email: stevemp@bcm.tmc.edu

©2007 Ethis Communications, Inc. *The Ocular Surface* ISSN: 1542-0124. (No authors listed). Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). 2007;5(2):163-178.

I. INTRODUCTION

This report summarizes the management and therapeutic options for treating dry eye disease. The level of evidence for supporting data from the literature is evaluated according to the modified American Academy of Ophthalmology Preferred Practices guidelines (Table 1).

II. GOALS OF THE MANAGEMENT AND THERAPY SUBCOMMITTEE

Goals of this committee were to identify appropriate therapeutic methods for the management of dry eye disease and recommend a sequence or strategy for their application, based on evidence-based review of the literature.

The quality of the evidence in the literature was graded according to a modification of the scheme used in the American Academy of Ophthalmology Preferred Practice Patterns series. When possible, peer-reviewed full publications, not abstracts, were used. The report was reviewed

Table 1. Evidence grading scheme

Clinical Studies

Level 1. Evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial, or evidence from well-designed studies applying rigorous statistical approaches.

Level 2. Evidence obtained from one of the following: a well-designed controlled trial without randomization, a well-designed cohort or case-control analytic study, preferably from one or more center, or a well-designed study accessible to more rigorous statistical analysis.

Level 3. Evidence obtained from one of the following: descriptive studies, case reports, reports of expert committees, expert opinion.

Basic Science Studies

Level 1. Well-performed studies confirming a hypothesis with adequate controls published in a high-impact journal.

Level 2. Preliminary or limited published study.

Level 3. Meeting abstracts or unpublished presentations.

This evidence grading scheme is based on that used in the American Academy of Ophthalmology Preferred Practice Pattern series.

OUTLINE

- I. Introduction
- II. Goals of the Management and Therapy Subcommittee
- III. Assessment of current dry eye therapies
 - A. Tear supplementation: lubricants
 - 1. General characteristics and effects
 - 2. Preservatives
 - 3. Electrolyte composition
 - 4. Osmolarity
 - 5. Viscosity agents
 - 6. Summary
 - B. Tear Retention
 - 1. Punctal occlusion
 - a. Rationale
 - b. Types
 - c. Clinical studies
 - d. Indications and contraindications
 - e. Complications
 - f. Summary
 - 2. Moisture chamber spectacles
 - 3. Contact lenses
 - C. Tear stimulation: secretagogues
 - D. Biological tear substitutes
 - 1. Serum
 - 2. Salivary gland autotransplantation
 - E. Anti-inflammatory therapy
 - 1. Cyclosporine
 - 2. Corticosteroids
 - a. Clinical studies
 - b. Basic research
 - 3. Tetracyclines
 - a. Properties of tetracyclines and their derivatives
 - 1) Antibacterial properties
 - 2) Anti-inflammatory
 - 3) Anti-angiogenic properties
 - b. Clinical applications of tetracycline
 - 1) Acne Rosacea
 - 2) Chronic posterior blepharitis: meibomianitis, meibomian gland dysfunction
 - 3) Dosage and safety
 - F. Essential fatty acids
 - G. Environmental strategies
- IV. Treatment recommendations
- V. Unanswered questions and future directions

III. ASSESSMENT OF CURRENT DRY EYE THERAPIES**A. Tear Supplementation: Lubricants****1. General Characteristics and Effects**

The term "artificial tears" is a misnomer for most products that identify themselves as such, because they do not mimic the composition of human tears. Most function as lubricants, although some more recent formulations mimic the electrolyte composition of human tears (TheraTears® [Advanced Vision Research, Woburn, MA]).^{1,2} The ocular lubricants presently available in the United States are approved based on the US Food and Drug Administration (FDA) monograph on over-the-counter (OTC) products (21 CFR 349) and are not based on clinical efficacy. The monograph specifies permitted active ingredients (eg, demulcents, emulsifiers, surfactants, and viscosity agents) and concentrations, but gives only limited guidance on inactive additives and solution parameters. Certain inactive ingredients that are used in artificial tears sold in the US (eg, castor oil in Endura™ [Allergan, Inc., Irvine, CA] and guar in Systane® [Alcon, Ft Worth, TX]) are not listed in the monograph.

It is difficult to prove that any ingredient in an ocular lubricant acts as an active agent. If there is an active ingredient, it is the polymeric base or viscosity agent, but this has proved difficult to demonstrate. This is either because it is not possible to detect the effects or differences in clinical trials with presently available clinical tests or because the currently available agents do not have any discernable clinical activity beyond a lubrication effect. Although certain artificial tears have demonstrated more success than others in reducing symptoms of irritation or decreasing ocular surface dye staining in head-to-head comparisons, there have been no large scale, masked, comparative clinical trials to evaluate the wide variety of ocular lubricants.

What is the clinical effect of ocular lubricants or artificial tears? Do they lubricate, replace missing tear constituents, reduce elevated tear film osmolarity, dilute or wash out inflammatory or inflammation-inducing agents? Do they, in some instances, actually wash out essential substances found in normal human tears? These questions remain to be answered as more sensitive clinical tests become available to detect changes in the ocular surface.

The foremost objectives in caring for patients with dry eye disease are to improve the patient's ocular comfort and quality of life, and to return the ocular surface and tear film to the normal homeostatic state. Although symptoms can rarely be eliminated, they can often be improved, leading to an improvement in the quality of life. It is more difficult to demonstrate that topical lubricants improve the ocular surface and the tear film abnormalities associated with dry eye. Most clinical studies fail to demonstrate significant correlation between symptoms and clinical test values or between the clinical test values themselves.³⁻⁵ It is not unusual for a dry eye with only mild symptoms to show significant rose bengal staining. Until agents are developed that can restore the ocular surface and tear film to their

by all subcommittee members and by the entire Dry Eye WorkShop membership. Comments and suggested revisions were discussed by the subcommittee members and incorporated into the report where deemed appropriate by consensus.

normal homeostatic state, the symptoms and signs of dry eye disease will continue.

Ocular lubricants are characterized by hypotonic or isotonic buffered solutions containing electrolytes, surfactants, and various types of viscosity agents. In theory, the ideal artificial lubricant should be preservative-free, contain potassium, bicarbonate, and other electrolytes and have a polymeric system to increase its retention time.^{1,6-8} Physical properties should include a neutral to slightly alkaline pH. Osmolarities of artificial tears have been measured to range from about 181 to 354 mOsm/L.⁹ The main variables in the formulation of ocular lubricants regard the concentration of and choice of electrolytes, the osmolarity and the type of viscosity/polymeric system, the presence or absence of preservative, and, if present, the type of preservative.

2. Preservatives

The single most critical advance in the treatment of dry eye came with the elimination of preservatives, such as benzalkonium chloride (BAK), from OTC lubricants. Because of the risk of contamination of multidose products, most either contain a preservative or employ some mechanism for minimizing contamination. The FDA has required that multidose artificial tears contain preservatives to prevent microbial growth.¹⁰ Preservatives are not required in unit dose vials that are discarded after a single use. The widespread availability of nonpreserved preparations allows patients to administer lubricants more frequently without concern about the toxic effects of preservatives. For patients with moderate-to-severe dry eye disease, the absence of preservatives is of more critical importance than the particular polymeric agent used in ocular lubricants. The ocular surface inflammation associated with dry eye is exacerbated by preserved lubricants; however, nonpreserved solutions are inadequate in themselves to improve the surface inflammation and epithelial pathology seen in dry eye disease.¹¹

Benzalkonium chloride is the most frequently used preservative in topical ophthalmic preparations, as well as in topical lubricants. Its epithelial toxic effects have been well established.¹²⁻¹⁷ The toxicity of BAK is related to its concentration, the frequency of dosing, the level or amount of tear secretion, and the severity of the ocular surface disease. In the patient with mild dry eye, BAK-preserved drops are usually well tolerated when used 4-6 times a day or less. In patients with moderate-to-severe dry eye, the potential for BAK toxicity is high, due to decreased tear secretion and decreased turnover.¹⁷ Some patients may be using other topical preparations (eg, glaucoma medications) that contain BAK, increasing their exposure to the toxic effects of BAK. Also, the potential for toxicity exists with patient abuse of other OTC products that contain BAK, such as vasoconstrictors.

BAK can damage the corneal and conjunctival epithelium, affecting cell-to-cell junctions and cell shape and microvilli, eventually leading to cell necrosis with sloughing of 1-2 layers of epithelial cells.¹⁷ Preservative-free formulations are absolutely necessary for patients with severe dry

eye with ocular surface disease and impairment of lacrimal gland secretion, or for patients on multiple, preserved topical medications for chronic eye disease. Patients with severe dry eye, greatly reduced tear secretion, and punctal occlusion are at particular risk for preservative toxicity. In such patients, the instilled agent cannot be washed out; if this risk has not been appreciated by the clinician, preserved drops might be used at high frequency.

Another additive used in OTC formulations is disodium (EDTA). It augments the preservative efficacy of BAK and other preservatives, but, by itself, it is not a sufficient preservative. Used in some nonpreserved solutions, it may help limit microbial growth in opened unit-dose vials. Although use of EDTA may allow a lower concentration of preservative, EDTA may itself be toxic to the ocular surface epithelium. A study comparing two preservative-free solutions, Hypotears PF[®] (Novartis Ophthalmics, East Hanover, NJ) containing EDTA and Refresh[®] (Allergan, Inc., Irvine, CA) without EDTA, showed that both formulations had identical safety profiles and were completely nontoxic to the rabbit corneal epithelium.¹⁸ Other studies found that EDTA-containing preparations increased corneal epithelial permeability.^{19,20} The potential exists that patients with severe dry eye will find that EDTA-containing preparations increase irritation.

Nonpreserved, single unit-dose tear substitutes are more costly for the manufacturer to produce, more costly for the patients to purchase, and less convenient to use than bottled ocular lubricants. For these reasons, reclosable unit dose vials (eg, Refresh Free [Allergan Inc., Irvine, CA]; Tears Natural Free[®] [Alcon, Fort Worth, TX]) were introduced. Less toxic preservatives, such as polyquad (polyquaternium-1), sodium chlorite (Purite[®]), and sodium perborate were developed to allow the use of multidose bottled lubricants and to avoid the known toxicity of BAK-containing solutions.^{21,22} The "vanishing" preservatives were sodium perborate and sodium chlorite (TheraTears[®] [Advanced Vision Research, Woburn, MA], Genteal[®] [Novartis, East Hanover, NJ], and Refresh Tears[®] [Allergan Inc., Irvine, CA]).

Sodium chlorite degrades to chloride ions and water upon exposure to UV light after instillation. Sodium perborate is converted to water and oxygen on contact with the tear film. For patients with severe dry eye, even vanishing preservatives may not totally degrade, due to a decrease in tear volume, and may be irritating. Patients prefer bottled preparations for reasons of both cost and ease of use. The ideal lubricant would come in a multidose, easy-to-use bottle that contains a preservative that completely dissipates before reaching the tear film, or is completely nontoxic and nonirritating and maintains absolute sterility with frequent use. One such multi-use, preservative-free product has been introduced to the market (Visine Pure-Tears[®] [Pfizer, Inc, NJ]).

Ocular ointments and gels are also used in treatment of dry eye disease. Ointments are formulated with a specific mixture of mineral oil and petrolatum. Some contain lanolin,

which can be irritating to the eye and delay corneal wound healing.²³ Individuals with sensitivity to wool may also be sensitive to lanolin.²³ Some ointments contain parabens as preservatives, and these ointments are not well tolerated by patients with severe dry eye. In general, ointments do not support bacterial growth and, therefore, do not require preservatives. Gels containing high molecular weight cross-linked polymers of acrylic acid (carbomers) have longer retention times than artificial tear solutions, but have less visual blurring effect than petrolatum ointments.

3. Electrolyte Composition

Solutions containing electrolytes and or ions have been shown to be beneficial in treating ocular surface damage due to dry eye.^{1,6,20,24,25} To date, potassium and bicarbonate seem to be the most critical. Potassium is important to maintain corneal thickness.⁷ In a dry-eye rabbit model, a hypotonic tear-matched electrolyte solution (TheraTears® [Advanced Vision Research, Woburn, MA]) increased conjunctival goblet cell density and corneal glycogen content, and reduced tear osmolarity and rose bengal staining after 2 weeks of treatment.²⁵ The restoration of conjunctival goblet cells seen in the dry-eye rabbit model has been corroborated in patients with dry eye after LASIK.²⁶

Bicarbonate-containing solutions promote the recovery of epithelial barrier function in damaged corneal epithelium and aid in maintaining normal epithelial ultrastructure. They may also be important for maintaining the mucin layer of the tear film.⁶ Ocular lubricants are available that mimic the electrolyte composition of human tears, eg, TheraTears® (Advanced Vision Research, Woburn, MA) and BION Tears® (Alcon, Fort Worth, TX).^{1,2} These also contain bicarbonate, which is critical for forming and maintaining the protective mucin gel in the stomach.²⁷ Bicarbonate may play a similar role for gel-forming mucins on the ocular surface. Because bicarbonate is converted to carbon dioxide when in contact with air and can diffuse through the plastic unit dose vials, foil packaging of the plastic vials is required to maintain stability.

4. Osmolarity

Tears of patients with dry eye have a higher tear film osmolarity (crystalloid osmolarity) than do those of normal patients.^{28,29} Elevated tear film osmolarity causes morphological and biochemical changes to the corneal and conjunctival epithelium^{18,30} and is pro-inflammatory.³¹ This knowledge influenced the development of hypo-osmotic artificial tears such as Hypotears® (230 mOsm/L [Novartis Ophthalmics, East Hanover, NJ]) and subsequently TheraTears® (181 mOsm/L [Advance Vision Research, Woburn, MA]).³²

Colloidal osmolality is another factor that varies in artificial tear formulations. While crystalloid osmolarity is related to the presence of ions, colloidal osmolality is dependent largely on macromolecule content. Colloidal osmolality, also known as *oncotic pressure*, is involved in the control of water transport in tissues. Differences in colloidal

osmolality affect the net water flow across membranes, and water flow is eliminated by applying hydrostatic pressure to the downside of the water flow. The magnitude of this osmotic pressure is determined by osmolality differences on the two sides of the membrane. Epithelial cells swell due to damage to their cellular membranes or due to a dysfunction in the pumping mechanism. Following the addition of a fluid with a high colloidal osmolality to the damaged cell surface, deturgescence occurs, leading to a return of normal cell physiology. Theoretically, an artificial tear formulation with a high colloidal osmolality may be of value. Holly and Esquivel evaluated many different artificial tear formulations and showed that Hypotears® (Novartis Ophthalmics, East Hanover, NJ) had the highest colloidal osmolality of all of the formulations tested.³³ Formulations with higher colloidal osmolality have since been marketed (Dwelle® [Dry Eye Company, Silverdale, WA]).

Protection against the adverse effects of increased osmolarity (osmoprotection) has led to development of OTC drops incorporating compatible solutes (such as glycerin, erythritol, and levocarnitine (Optive® [Allergan Inc., Irvine, CA])). It is thought that the compatible solutes distribute between the tears and the intracellular fluids to protect against potential cellular damage from hyperosmolar tears.³⁴

5. Viscosity Agents

The stability of the tear film depends on the chemical-physical characteristics of that film interacting with the conjunctival and corneal epithelium via the membrane-spanning mucins (ie, MUC-16 and MUC-4). In the classical three-layered tear film model, the mucin layer is usually thought of as a surfactant or wetting agent, acting to lower the surface tension of the relatively hydrophobic ocular surface, rendering the corneal and conjunctival cells “wetable.”³³ Currently, the tear film is probably best described as a hydrated, mucin gel whose mucin concentration decreases with distance from the epithelial cell surface. It may have a protective role similar to that of mucin in the stomach.³⁵ It may also serve as a “sink” or storage vehicle for substances secreted by the main and accessory lacrimal glands and the ocular surface cells. This may explain why most of the available water-containing lubricants are only minimally effective in restoring the normal homeostasis of the ocular surface. In addition to washing away and diluting out irritating or toxic substances in the tear film, artificial lubricants hydrate gel-forming mucin. While some patients with dry eye have decreased aqueous lacrimal gland secretion, alterations or deficiencies involving mucin also cause dry eye.

Macromolecular complexes added to artificial lubricants act as viscosity agents. The addition of a viscosity agent increases residence time, providing a longer interval of patient comfort. For example, when a viscous, anionic charged carboxymethyl-cellulose (CMC, 100,000 mw) solution was compared with a neutral hydroxymethylcellulose (HPMC) solution, CMC was shown to have a significantly slower rate of clearance from the eye.³⁶ Viscous agents in active drug

formulations may also prolong ocular surface contact, increasing the duration of action and penetration of the drug.

Viscous agents may also protect the ocular surface epithelium. It is known that rose bengal stains abnormal corneal and conjunctival epithelial cells expressing an altered mucin glycoalyx.³⁷ Agents such as hydroxymethylcellulose (HMC), which decrease rose bengal staining in dry eye subjects,³⁸ may either “coat and protect” the surface epithelium or help restore the protective effect of mucins.

In the US, carboxymethyl cellulose is the most commonly used polymeric viscosity agent (IRI Market Share Data, Chicago, IL), typically in concentrations from 0.25% to 1%, with differences in molecular weight also contributing to final product viscosity. Carboxymethyl cellulose has been found to bind to and be retained by human epithelial cells.³⁹ Other viscosity agents included in the FDA monograph (in various concentrations) include polyvinyl alcohol, polyethylene glycol, glycol 400, propylene glycol hydroxymethyl cellulose and hydroxypropyl cellulose.

The blurring of vision and esthetic disadvantages of caking and drying on eyelashes are drawbacks of highly viscous agents that patients with mild to moderate dry eye will not tolerate. Lower molecular-weight viscous agents help to minimize these problems. Because patient compliance, comfort, and convenience are important considerations, a range of tear substitute formulations with varying viscosities are needed.

Hydroxypropyl-guar (HP-guar) has been used as a gelling agent in a solution containing glycol 400 and propylene glycol (Systane[®], Alcon, Fort Worth, TX). It has been suggested that HP-guar preferentially binds to the more hydrophobic, desiccated or damaged areas of the surface epithelial cells, providing temporary protection for these cells.^{40,41} Several commercial preparations containing oil in the form of castor oil (Endura[™] [Allergan Inc., Irvine, CA]) or mineral oil (Soothe[®] [Bausch & Lomb, Rochester, NY]) are purported to aid in restoring or increasing the lipid layer of the tear film.^{42,43} Hyaluronic acid is a viscosity agent that has been investigated for years as an “active” compound added to tear substitute formulations for the treatment of dry eye. Hyaluronic acid (0.2%) has significantly longer ocular surface residence times than 0.3 percent HPMC or 1.4 percent polyvinyl alcohol.⁴⁴ Some clinical studies reported improvement in⁴⁴⁻⁴⁸ dry eye in patients treated with sodium hyaluronate-containing solutions compared to other lubricant solutions, whereas others did not.⁴⁸ Although lubricant preparations containing sodium hyaluronate have not been approved for use in the US, they are frequently used in some countries.

6. Summary

Although many topical lubricants, with various viscosity agents, may improve symptoms and objective findings, there is no evidence that any agent is superior to another. Most clinical trials involving topical lubricant preparations will document some improvement (but not resolution) of subjective symptoms and improvement in some objective

parameters.⁴ However, the improvements noted are not necessarily any better than those seen with the vehicle or other nonpreserved artificial lubricants. The elimination of preservatives and the development of newer, less toxic preservatives have made ocular lubricants better tolerated by dry eye patients. However, ocular lubricants, which have been shown to provide some protection of the ocular surface epithelium and some improvement in patient symptoms and objective findings, have not been demonstrated in controlled clinical trials to be sufficient to resolve the ocular surface disorder and inflammation seen in most dry eye sufferers.

B. Tear Retention

1. Punctal Occlusion

a. Rationale

While the concept of permanently occluding the lacrimal puncta with cautery to treat dry eye extends back 70 years,⁴⁹ and, although the first dissolvable implants were used 45 years ago,⁵⁰ the modern era of punctal plug use began in 1975 with the report by Freeman.⁵¹ Freeman described the use of a dumbbell-shaped silicone plug, which rests on the opening of the punctum and extends into the canaliculus. His report established a concept of punctal occlusion, which opened the field for development of a variety of removable, long-lasting plugs to retard tear clearance in an attempt to treat the ocular surface of patients with deficient aqueous tear production. The Freeman style plug remains the prototype for most styles of punctal plugs.

b. Types

Punctal plugs are divided into two main types: absorbable and nonabsorbable. The former are made of collagen or polymers and last for variable periods of time (3 days to 6 months). The latter nonabsorbable “permanent” plugs include the Freeman style, which consists of a surface collar resting on the punctal opening, a neck, and a wider base. In contrast, the Herrick plug (Lacrimedics [Eastsound, WA]) is shaped like a golf tee and is designed to reside within the canaliculus. It is blue for visualization; other variations are radiopaque. A newly designed cylindrical Smartplug[™] (Medennium Inc [Irvine, CA]) expands and increases in diameter in situ following insertion into the canaliculus due to thermodynamic properties of its hydrophilic acrylic composition.

c. Clinical Studies

A variety of clinical studies evaluating the efficacy of punctal plugs have been reported.⁵²⁻⁵⁶ These series generally fall into Level II evidence. Their use has been associated with objective and subjective improvement in patients with both Sjogren and non-Sjogren aqueous tear deficient dry eye, filamentary keratitis, contact lens intolerance, Stevens-Johnson disease, severe trachoma, neurotrophic keratopathy, post-penetrating keratoplasty, diabetic keratopathy, and post-photorefractive keratectomy or laser in situ keratomileusis. Several studies have been performed

to evaluate the effects of punctal plugs on the efficacy of glaucoma medications in reducing intraocular pressure, and these studies have reported conflicting results.^{57,58} Beneficial outcome in dry eye symptoms has been reported in 74-86% of patients treated with punctal plugs. Objective indices of improvement reported with the use of punctal plugs include improved corneal staining, prolonged tear film breakup time (TFBUT), decrease in tear osmolarity, and increase in goblet cell density. Overall, the clinical utility of punctal plugs in the management of dry eye disease has been well documented.

d. Indications and Contraindications

In a recent review on punctal plugs, it was reported that in a major eye clinic, punctal plugs are considered indicated in patients who are symptomatic of dry eyes, have a Schirmer test (with anesthesia) result less than 5 mm at 5 minutes, and show evidence of ocular surface dye staining.⁵⁶

Contraindications to the use of punctal plugs include allergy to the materials used in the plugs to be implanted, punctal ectropion, and pre-existing nasolacrimal duct obstruction, which would, presumably, negate the need for punctal occlusion. It has been suggested that plugs may be contraindicated in dry eye patients with clinical ocular surface inflammation, because occlusion of tear outflow would prolong contact of the abnormal tears containing proinflammatory cytokines with the ocular surface. Treatment of the ocular surface inflammation prior to plug insertion has been recommended. Acute or chronic infection of the lacrimal canaliculus or lacrimal sac is also a contraindication to use of a plug.

e. Complications

The most common complication of punctal plugs is spontaneous plug extrusion, which is particularly common with the Freeman-style plugs. Over time, an extrusion rate of 50% has been reported, but many of these extrusions took place after extensive periods of plug residence. Most extrusions are of small consequence, except for inconvenience and expense. More troublesome complications include internal migration of a plug, biofilm formation and infection,⁵⁹ and pyogenic granuloma formation. Removal of migrated canalicular plugs can be difficult and may require surgery to the nasolacrimal duct system.^{60,61}

f. Summary

The extensive literature on the use of punctal plugs in the management of dry eye disease has documented their utility. Several recent reports, however, have suggested that absorption of tears by the nasolacrimal ducts into surrounding tissues and blood vessels may provide a feedback mechanism to the lacrimal gland regulating tear production.⁶² In one study, placement of punctal plugs in patients with normal tear production caused a significant decrease in tear production for up to 2 weeks after plug insertion.⁶³ This cautionary note should be considered when deciding

whether to incorporate punctal occlusion into a dry eye disease management plan.

2. Moisture Chamber Spectacles

The wearing of moisture-conserving spectacles has for many years been advocated to alleviate ocular discomfort associated with dry eye. However, the level of evidence supporting its efficacy for dry eye treatment has been relatively limited. Tsubota et al, using a sensitive moisture sensor, reported an increase in periocular humidity in subjects wearing such spectacles.⁶⁴ Addition of side panels to the spectacles was shown to further increase the humidity.⁶⁵ The clinical efficacy of moisture chamber spectacles has been reported in case reports.^{66,67} Kurihashi proposed a related treatment for dry eye patients, in the form of a wet gauze eye mask.⁶⁸ Conversely, Nichols et al recently reported in their epidemiologic study that spectacle wearers were twice as likely as emmetropes to report dry eye disease.⁶⁹ The reason for this observation was not explained.

There have been several reports with relatively high level of evidence describing the relationship between environmental humidity and dry eye. Korb et al reported that increases in periocular humidity caused a significant increase in thickness of the tear film lipid layer.⁷⁰ Dry eye subjects wearing spectacles showed significantly longer interblink intervals than those who did not wear spectacles, and duration of blink (blinking time) was significantly longer in the latter subjects.⁷⁰ Instillation of artificial tears caused a significant increase in the interblink interval and a decrease in the blink rate.⁷¹ Maruyama et al reported that dry eye symptoms worsened in soft contact lens wearers when environmental humidity decreased.⁷²

3. Contact Lenses

Contact lenses may help to protect and hydrate the corneal surface in severe dry eye conditions. Several different contact lens materials and designs have been evaluated, including silicone rubber lenses and gas permeable scleral-bearing hard contact lenses with or without fenestration.⁷³⁻⁷⁷ Improved visual acuity and comfort, decreased corneal epitheliopathy, and healing of persistent corneal epithelial defects have been reported.⁷³⁻⁷⁷ Highly oxygen-permeable materials enable overnight wear in appropriate circumstances.⁷⁵ There is a small risk of corneal vascularization and possible corneal infection associated with the use of contact lenses by dry eye patients.

C. Tear Stimulation: Secretagogues

Several potential topical pharmacologic agents may stimulate aqueous secretion, mucous secretion, or both. The agents currently under investigation by pharmaceutical companies are diquafosol (one of the P2Y2 receptor agonists), rebamipide, gefarnate, ecabet sodium (mucous secretion stimulants), and 15(S)-HETE (MUC1 stimulant). Among them, a diquafosol eye drop has been favorably evaluated in clinical trials. 2% diquafosol (INS365, DE-089 [Santen, Osaka, Japan]; Inspire [Durham, NC]) proved to

be effective in the treatment of dry eye in a randomized, double-masked trial in humans to reduce ocular surface staining.⁷⁸ A similar study demonstrated the ocular safety and tolerability of diquafosol in a double-masked, placebo-controlled, randomized study.⁷⁹ This agent is capable of stimulating both aqueous and mucous secretion in animals and humans.⁸⁰⁻⁸³ Beneficial effects on corneal epithelial barrier function, as well as increased tear secretion, has been demonstrated in the rat dry eye model.⁸⁴ Diquafosol also has been shown to stimulate mucin release from goblet cells in a rabbit dry eye model.^{85,86}

The effects of rebamipide (OPC-12759 [Otsuka, Rockville, MD]; Novartis [Basel, Switzerland]) have been evaluated in human clinical trials. In animal studies, rebamipide increased the mucin-like substances on the ocular surface of N-acetylcysteine-treated rabbit eyes.⁸⁷ It also had hydroxyl radical scavenging effects on UVB-induced corneal damage in mice.⁸⁸

Ecabet sodium (Senju [Osaka, Japan]; ISTA [Irvine, CA]) is being evaluated in clinical trials internationally, but only limited results have yet been published. A single instillation of ecabet sodium ophthalmic solution elicited a statistically significant increase in tear mucin in dry eye patients.⁸⁹ Gefarnate (Santen [Osaka, Japan]) has been evaluated in animal studies. Gefarnate promoted mucin production after conjunctival injury in monkeys.⁹⁰ Gefarnate increased PAS-positive cell density in rabbit conjunctiva and stimulated mucin-like glycoprotein stimulation from rat cultured corneal epithelium.^{91,92} An *in vivo* rabbit experiment showed a similar result.^{93,94}

The agent 15(S)-HETE, a unique molecule, can stimulate MUC1 mucin expression on ocular surface epithelium.⁹⁵ 15(S)-HETE protected the cornea in a rabbit model of desiccation-induced injury, probably because of mucin secretion.⁹⁶ It has been shown to have beneficial effects on secretion of mucin-like glycoprotein by the rabbit corneal epithelium.⁹⁷ Other laboratory studies confirm the stimulatory effect of 15(S)-HETE.⁹⁸⁻¹⁰¹ Some of these agents may become useful clinical therapeutic modalities in the near future.

Two orally administered cholinergic agonists, pilocarpine and cevilemine, have been evaluated in clinical trials for treatment of Sjogren syndrome associated keratoconjunctivitis sicca (**KCS**). Patients who were treated with pilocarpine at a dose of 5 mg QID experienced a significantly greater overall improvement than placebo-treated patients in "ocular problems" in their ability to focus their eyes during reading, and in symptoms of blurred vision compared with placebo-treated patients.¹⁰² The most commonly reported side effect from this medication was excessive sweating, which occurred in over 40% of patients. Two percent of the patients taking pilocarpine withdrew from the study because of drug-related side effects. Other studies have reported efficacy of pilocarpine for ocular signs and symptoms of Sjogren syndrome KCS,¹⁰³⁻¹⁰⁵ including an increase in conjunctival goblet cell density after 1 and 2 months of therapy.¹⁰⁶

Cevilemine is another oral cholinergic agonist that was found to significantly improve symptoms of dryness and aqueous tear production and ocular surface disease compared to placebo when taken in doses of 15 or 30 mg TID.^{107,108} This agent may have fewer adverse systemic side effects than oral pilocarpine.

D. Biological Tear Substitutes

Naturally occurring biological, ie, nonpharmaceutical fluids, can be used to substitute for natural tears. The use of serum or saliva for this purpose has been reported in humans. They are usually unpreserved. When of autologous origin, they lack antigenicity and contain various epitheliotropic factors, such as growth factors, neurotrophins, vitamins, immunoglobulins, and extracellular matrix proteins involved in ocular surface maintenance. Biological tear substitutes maintain the morphology and support the proliferation of primary human corneal epithelial cells better than pharmaceutical tear substitutes.¹⁰⁹ However, despite biomechanical and biochemical similarities, relevant compositional differences compared with normal tears exist and are of clinical relevance.¹¹⁰ Additional practical problems concern sterility and stability, and a labor-intensive production process or a surgical procedure (saliva) is required to provide the natural tear substitute to the ocular surface.

1. Serum

Serum is the fluid component of full blood that remains after clotting. Its topical use for ocular surface disease was much stimulated by Tsubota's prolific work in the late 1990s.¹¹¹ The practicalities and published evidence of autologous serum application were recently reviewed.¹¹² The use of blood and its components as a pharmaceutical preparation in many countries is restricted by specific national laws. To produce serum eye drops and to use them for outpatients, a license by an appropriate national body may be required in certain countries. The protocol used for the production of serum eye drops determines their composition and efficacy. An optimized protocol for the production was recently published.¹¹³ Concentrations between 20% and 100% of serum have been used. The efficacy seems to be dose-dependent.

Because of significant variations in patient populations, production and storage regimens, and treatment protocols, the efficacy of serum eye drops in dry eyes has varied substantially between studies.¹¹³ Three published prospective randomized studies with similar patient populations (predominantly immune disease associated dry eye, ie, Sjogren syndrome) are available. When comparing 20% serum with 0.9% saline applied 6 times per day, Tananuvat et al found only a trend toward improvement of symptoms and signs of dry eyes,¹¹⁴ whereas Kojima et al reported significant improvement of symptom scores, fluorescein-breakup time (**FBUT**), and fluorescein and rose bengal staining.¹¹⁵

A prospective clinical cross-over trial compared 50% serum eyedrops against the commercial lubricant previously

used by each patient. Symptoms improved in 10 out of 16 patients, and impression cytological findings improved in 12 out of 25 eyes.¹¹⁶ Noda-Tsuruya and colleagues found that 20% autologous serum significantly improved TFBUT and decreased conjunctival rose bengal and cornea fluorescein staining 1-3 months postoperatively, compared to treatment with artificial tears, which did not change these parameters.¹¹⁷ Additional reports of successful treatment of persistent epithelial defects—where success is more clearly defined as “healing of the defect”—with autologous serum substantiate the impression that this is a valuable therapeutic option for ocular surface disease.¹¹⁸

2. Salivary Gland Autotransplantation

Salivary submandibular gland transplantation is capable of replacing deficient mucin and the aqueous tear film phase. This procedure requires collaboration between an ophthalmologist and a maxillofacial surgeon. With appropriate microvascular anastomosis, 80% of grafts survive. In patients with absolute aqueous tear deficiency, viable submandibular gland grafts, in the long-term, provide significant improvement of Schirmer test FBUT, and rose bengal staining, as well as reduction of discomfort and the need for pharmaceutical tear substitutes. Due to the hypo-osmolality of saliva, compared to tears, excessive salivary tearing can induce a microcystic corneal edema, which is temporary, but can lead to epithelial defects.¹¹⁰ Hence, this operation is indicated only in end-stage dry eye disease with an absolute aqueous tear deficiency (Schirmer-test wetting of 1 mm or less), a conjunctivalized surface epithelium, and persistent severe pain despite punctal occlusion and at least hourly application of unpreserved tear substitutes. For this group of patients, such surgery is capable of substantially reducing discomfort, but often has no effect on vision.^{119,120}

E. Anti-Inflammatory Therapy

Disease or dysfunction of the tear secretory glands leads to changes in tear composition, such as hyperosmolality, that stimulate the production of inflammatory mediators on the ocular surface.^{31,121} Inflammation may, in turn, cause dysfunction or disappearance of cells responsible for tear secretion or retention.¹²² Inflammation can also be initiated by chronic irritative stress (eg, contact lenses) and systemic inflammatory/autoimmune disease (eg, rheumatoid arthritis). Regardless of the initiating cause, a vicious circle of inflammation can develop on the ocular surface in dry eye that leads to ocular surface disease. Based on the concept that inflammation is a key component of the pathogenesis of dry eye, the efficacy of a number of anti-inflammatory agents for treatment of dry eye disease has been evaluated in clinical trials and animal models.

1. Cyclosporine

The potential of cyclosporine-A (**CsA**) for treating dry eye disease was initially recognized in dogs that develop spontaneous KCS.¹²³ The therapeutic efficacy of CsA for human KCS was then documented in several small, single-

center, randomized, double-masked clinical trials.^{124,125} CsA emulsion for treatment of KCS was subsequently evaluated in several large multicenter, randomized, double-masked clinical trials.

In a Phase 2 clinical trial, four concentrations of CsA (0.05%, 0.1%, 0.2%, or 0.4%) administered twice daily to both eyes of 129 patients for 12 weeks was compared to vehicle treatment of 33 patients.¹²⁶ CsA was found to significantly decrease conjunctival rose bengal staining, superficial punctate keratitis, and ocular irritation symptoms (sandy or gritty feeling, dryness, and itching) in a subset of 90 patients with moderate-to-severe KCS. There was no clear dose response; CsA 0.1% produced the most consistent improvement in objective endpoints, whereas CsA 0.05% gave the most consistent improvement in patient symptoms (Level I).

Two independent Phase 3 clinical trials compared twice-daily treatment with 0.05% or 0.1% CsA or vehicle in 877 patients with moderate-to-severe dry eye disease.¹²⁷ When the results of the two Phase 3 trials were combined for statistical analysis, patients treated with CsA, 0.05% or 0.1%, showed significantly ($P < 0.05$) greater improvement in two objective signs of dry eye disease (corneal fluorescein staining and anesthetized Schirmer test values) compared to those treated with vehicle. An increased Schirmer test score was observed in 59% of patients treated with CsA, with 15% of patients having an increase of 10 mm or more. In contrast, only 4% of vehicle-treated patients had this magnitude of change in their Schirmer test scores ($P < 0.0001$).

CsA 0.05% treatment also produced significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision symptoms, need for concomitant artificial tears, and the global response to treatment). No dose-response effect was noted. Both doses of CSA exhibited an excellent safety profile with no significant systemic or ocular adverse events, except for transient burning symptoms after instillation in 17% of patients. Burning was reported in 7% of patients receiving the vehicle. No CsA was detected in the blood of patients treated with topical CsA for 12 months. Clinical improvement from CsA that was observed in these trials was accompanied by improvement in other disease parameters. Treated eyes had an approximately 200% increase in conjunctival goblet cell density.¹²⁸ Furthermore, there was decreased expression of immune activation markers (ie, HLA-DR), apoptosis markers (ie, Fas), and the inflammatory cytokine IL-6 by the conjunctival epithelial cells.^{129,130} The numbers of CD3-, CD4-, and CD8-positive T lymphocytes in the conjunctiva decreased in cyclosporine-treated eyes, whereas vehicle-treated eyes showed an increased number of cells expressing these markers.¹³¹ After treatment with 0.05% cyclosporine, there was a significant decrease in the number of cells expressing the lymphocyte activation markers CD11a and HLA-DR, indicating less activation of lymphocytes compared with vehicle-treated eyes.

Two additional immunophilins, pimecrolimus and tacrolimus, have been evaluated in clinical trials of KCS.

2. Corticosteroids

a. Clinical Studies

Corticosteroids are an effective anti-inflammatory therapy in dry eye disease. Level I evidence is published for a number of corticosteroid formulations. In a 4-week, double-masked, randomized study in 64 patients with KCS and delayed tear clearance, loteprednol etabonate 0.5% ophthalmic suspension (Lotemax [Bausch and Lomb, Rochester, NY]), q.i.d., was found to be more effective than its vehicle in improving some signs and symptoms.¹³²

In a 4-week, open-label, randomized study in 32 patients with KCS, patients receiving fluorometholone plus artificial tear substitutes (ATS) experienced lower symptom severity scores and lower fluorescein and rose bengal staining than patients receiving either ATS alone or ATS plus flurbiprofen.¹³³

A prospective, randomized clinical trial compared the severity of ocular irritation symptoms and corneal fluorescein staining in two groups of patients, one treated with topical nonpreserved methylprednisolone for 2 weeks, followed by punctal occlusion (Group 1), with a group that received punctal occlusion alone (Group 2).¹³⁴ After 2 months, 80% of patients in Group 1 and 33% of patients in Group 2 had complete relief of ocular irritation symptoms. Corneal fluorescein staining was negative in 80% of eyes in Group 1 and 60% of eyes in Group 2 after 2 months. No steroid-related complications were observed in this study.

Level III evidence is also available to support the efficacy of corticosteroids. In an open-label, non-comparative trial, extemporaneously formulated nonpreserved methylprednisolone 1% ophthalmic suspension was found to be clinically effective in 21 patients with Sjogren syndrome KCS.¹³⁵ In a review, it was stated that "...clinical improvement of KCS has been observed after therapy with anti-inflammatory agents, including corticosteroids."¹³⁶

In the US Federal Regulations, ocular corticosteroids receiving "class labeling" are indicated for the treatment "...of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation." We interpret that KCS is included in this list of steroid-responsive inflammatory conditions.¹³⁷⁻¹⁴⁰

b. Basic Research

Corticosteroids are the standard anti-inflammatory agent for numerous basic research studies of inflammation, including the types that are involved in KCS. The corticosteroid methylprednisolone was noted to preserve corneal epithelial smoothness and barrier function in an experimental murine model of dry eye.¹⁴¹ This was attributed to its ability to maintain the integrity of corneal epithelial tight junctions and decrease desquamation of apical corneal epithelial cells.¹⁴² A concurrent study showed

that methylprednisolone prevented an increase in MMP-9 protein in the corneal epithelium, as well as gelatinase activity in the corneal epithelium and tears in response to experimental dry eye.¹⁴¹

Preparations of topically applied androgen and estrogen steroid hormones are currently being evaluated in randomized clinical trials. A trial of topically applied 0.03% testosterone was reported to increase the percentage of patients that had meibomian gland secretions with normal viscosity and to relieve discomfort symptoms after 6 months of treatment compared to vehicle.¹⁴³ TFBUT and lipid layer thickness were observed to increase in a patient with KCS who was treated with topical androgen for 3 months.¹⁴⁴ Tear production and ocular irritation symptoms were reported to increase following treatment with topical 17 beta-oestradiol solution for 4 months.¹⁴⁵

3. Tetracyclines

a. Properties of Tetracyclines and Their Derivatives

1) Antibacterial Properties

The antimicrobial effect of oral tetracycline treatment analogues (eg, minocycline, doxycycline) has previously been discussed by Shine et al,¹⁴⁶ Dougherty et al,¹⁴⁷ and Ta et al.¹⁴⁸ It is hypothesized that a decrease in bacterial flora producing lipolytic exoenzymes^{146,148} and inhibition of lipase production¹⁴⁷ with resultant decrease in meibomian lipid breakdown products¹⁴⁶ may contribute to improvement in clinical parameters in dry eye-associated diseases.

2) Anti-Inflammatory Properties

The tetracyclines have anti-inflammatory as well as antibacterial properties that may make them useful for the management of chronic inflammatory diseases. These agents decrease the activity of collagenase, phospholipase A₂, and several matrix metalloproteinases, and they decrease the production of interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha in a wide range of tissues, including the corneal epithelium.¹⁴⁹⁻¹⁵¹ At high concentrations, tetracyclines inhibit staphylococcal exotoxin-induced cytokines and chemokines.^{152,153}

3) Anti-angiogenic Properties

Angiogenesis, the formation of new blood vessels, occurs in many diseases. These include benign conditions (eg, rosacea) and malignant processes (eg, cancer). Minocycline and doxycycline inhibit angiogenesis induced by implanted tumors in rabbit cornea.¹⁵⁴ The anti-angiogenic effect of tetracycline may have therapeutic implications in inflammatory processes accompanied by new blood vessel formation. Well-controlled studies must be performed, at both the laboratory and clinical levels, to investigate this potential.¹⁵⁵

b. Clinical Applications of Tetracycline

1) Acne Rosacea

Rosacea, including its ocular manifestations, is an inflammatory disorder, occurring mainly in adults, with peak severity in the third and fourth decades. Current recom-

mendations are to treat rosacea with long-term doxycycline, minocycline, tetracycline, or erythromycin.¹⁵⁶ These recommendations may be tempered by certain recent reports that in women, the risk of developing breast cancer and of breast cancer morbidity increases cumulatively with duration of antibiotic use, including tetracyclines.^{157,158} Another large study did not substantiate these findings.¹⁵⁹

Tetracyclines and their analogues are effective in the treatment of ocular rosacea,^{160,161} for which a single daily dose of doxycycline may be effective.¹⁶² In addition to the anti-inflammatory effects of tetracyclines, their ability to inhibit angiogenesis may contribute to their effectiveness in rosacea-related disorders. Factors that promote angiogenesis include protease-triggered release of angiogenic factors stored in the extracellular matrix, inactivation of endothelial growth factor inhibitors, and release of angiogenic factors from activated macrophages.^{155,163}

Tetracyclines are also known to inhibit matrix metalloproteinase expression, suggesting a rationale for their use in ocular rosacea.¹⁶⁴ Although tetracyclines have been used for management of this disease, no randomized, placebo-controlled, clinical trials have been performed to assess their efficacy.¹⁵³

2) Chronic Posterior Blepharitis: Meibomianitis, Meibomian Gland Dysfunction

Chronic blepharitis is typically characterized by inflammation of the eyelids. There are multiple forms of chronic blepharitis, including staphylococcal, seborrheic (alone, mixed seborrheic/staphylococcal, seborrheic with meibomian seborrhea, seborrheic with secondary meibomitis), primary meibomitis, and others, like atopic, psoriatic, and fungal infections.¹⁶⁵ Meibomian gland dysfunction (**MGD**) has been associated with apparent aqueous-deficient dry eye. Use of tetracycline in patients with meibomianitis has been shown to decrease lipase production by tetracycline-sensitive as well as resistant strains of staphylococci. This decrease in lipase production was associated with clinical improvement.¹⁴⁷ Similarly, minocycline has been shown to decrease the production of diglycerides and free fatty acids in meibomian secretions. This may be due to lipase inhibition by the antibiotic or a direct effect on the ocular flora.¹⁴⁶ One randomized, controlled clinical trial of tetracycline in ocular rosacea compared symptom improvement in 24 patients treated with either tetracycline or doxycycline.¹⁶⁶ All but one patient reported an improvement in symptoms after 6 weeks of therapy. No placebo group was included in this trial.

A prospective, randomized, double-blind, placebo-controlled, partial crossover trial compared the effect of oxytetracycline to provide symptomatic relief of blepharitis with or without rosacea. Only 25% of the patients with blepharitis without rosacea responded to the antibiotic, whereas 50% responded when both diseases were present.¹⁶⁷ In another trial of 10 patients with both acne rosacea and concomitant meibomianitis, acne rosacea without concomitant ocular involvement, or seborrheic blepharitis, minocycline 50 mg daily for 2 weeks followed by 100 mg

daily for a total of 3 months significantly decreased bacterial flora ($P = 0.0013$). Clinical improvement was seen in all patients with meibomianitis.¹⁴⁸

Because of the improvement observed in small clinical trials of patients with meibomianitis, the American Academy of Ophthalmology recommends the chronic use of either doxycycline or tetracycline for the management of meibomianitis.¹⁶⁵ Larger randomized placebo-controlled trials assessing symptom improvement rather than surrogate markers are needed to clarify the role of this antibiotic in blepharitis treatment.¹⁵³ Tetracycline derivatives (eg, minocycline, doxycycline) have been recommended as treatment options for chronic blepharitis because of their high concentration in tissues, low renal clearance, long half-life, high level of binding to serum proteins, and decreased risk of photosensitization.¹⁶⁸

Several studies have described the beneficial effects of minocycline and other tetracycline derivatives (eg, doxycycline) in the treatment of chronic blepharitis.^{146,147,168,169} Studies have shown significant changes in the aqueous tear parameters, such as tear volume and tear flow, following treatment with tetracycline derivatives (eg, minocycline). One study also demonstrated a decrease in aqueous tear production that occurred along with clinical improvement.¹⁷⁰

A recently published randomized, prospective study by Yoo Se et al compared different doxycycline doses in 150 patients (300 eyes) who had chronic meibomian gland dysfunction and who did not respond to lid hygiene and topical therapy for more than 2 months.¹⁷¹ All topical therapy was stopped for at least 2 weeks prior to beginning the study. After determining the TFBUT and Schirmer test scores, patients were divided into three groups: a high dose group (doxycycline, 200 mg, twice a day), a low dose group (doxycycline, 20 mg, twice a day) and a control group (placebo). After one month, TFBUT, Schirmer scores, and symptoms improved. Both the high- and low-dose groups had statistically significant improvement in TFBUT after treatment. This implies that low-dose doxycycline (20 mg twice a day) therapy may be effective in patients with chronic meibomian gland dysfunction.

3) Dosage and Safety

Systemic administration of tetracyclines is widely recognized for the ability to suppress inflammation and improve symptoms of meibomianitis.^{172,173} The optimal dosing schedule has not been established; however, a variety of dose regimens have been proposed including 50 or 100 mg doxycycline once a day,¹⁷⁴ or an initial dose of 50 mg a day for the first 2 weeks followed by 100 mg a day for a period of 2.5 months, in an intermittent fashion.^{146-148,170} Others have proposed use of a low dose of doxycycline (20 mg) for treatment of chronic blepharitis on a long-term basis.¹⁷¹ The safety issues associated with long-term oral tetracycline therapy, including minocycline, are well known. Many management approaches have been suggested for the use of tetracycline and its derivatives; however, a safe but adequate option in management needs to be considered because of

Table 2. Dry eye severity grading scheme

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic occurs under environ stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying, chronic and/or constant limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+ / ++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

*Must have signs AND symptoms. TFBUT: fluorescein tear break-up time. MGD: meibomian gland disease

Reprinted with permission from Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. *Cornea* 2006;25:90-7

the new information regarding the potentially hazardous effects of prolonged use of oral antibiotics. A recent study suggested that a 3-month course of 100 mg of minocycline might be sufficient to bring significant meibomianitis under control, as continued control was maintained for at least 3 months after cessation of therapy.¹⁷⁰

In an experimental murine model of dry eye, topically applied doxycycline was found to preserve corneal epithelial smoothness and barrier function.¹⁴¹ It also preserved the integrity of corneal epithelial tight junctions in dry eyes, leading to a marked decrease in apical corneal epithelial cell desquamation.¹⁴² This corresponded to a decrease in MMP-9 protein in the corneal epithelium and reduced gelatinase activity in the corneal epithelium and tears.¹⁴¹

F. Essential Fatty Acids

Essential fatty acids are necessary for complete health. They cannot be synthesized by vertebrates and must be obtained from dietary sources. Among the essential fatty acids are 18 carbon omega-6 and omega-3 fatty acids. In the typical western diet, 20-25 times more omega-6 than omega-3 fatty acids are consumed. Omega-6 fatty acids are precursors for arachidonic acid and certain proinflammatory lipid mediators (PGE2 and LTB4). In contrast, certain omega-3 fatty acids (eg, EPA found in fish oil) inhibit the synthesis of these lipid mediators and block production of IL-1 and TNF-alpha.^{175,176}

A beneficial clinical effect of fish oil omega-3 fatty acids on rheumatoid arthritis has been observed in several

double-masked, placebo-controlled clinical trials.^{177,178} In a prospective, placebo-controlled clinical trial of the essential fatty acids, linoleic acid and gamma-linolenic acid administered orally twice daily produced significant improvement in ocular irritation symptoms and ocular surface lissamine green staining.¹⁷⁹ Decreased conjunctival HLA-DR staining also was observed.

G. Environmental Strategies

Factors that may decrease tear production or increase tear evaporation, such as the use of systemic anticholinergic medications (eg, antihistamines and antidepressants) and desiccating environmental stresses (eg, low humidity and air conditioning drafts) should be minimized or eliminated.¹⁸⁰⁻¹⁸² Video display terminals should be lowered below eye level to decrease the interpalpebral aperture, and patients should be encouraged to take periodic breaks with eye closure when reading or working on a computer.¹⁸³ A humidified environment is recommended to reduce tear evaporation. This is particularly beneficial in dry climates and high altitudes. Nocturnal lagophthalmos can be treated by wearing swim goggles, taping the eyelid closed, or tarsorrhaphy.

IV. TREATMENT RECOMMENDATIONS

In addition to material presented above, the subcommittee members reviewed the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force (ITF) Delphi Panel on dry

Table 3. Dry eye menu of treatments

Artificial tears substitutes
Gels/Ointments
Moisture chamber spectacles
Anti-inflammatory agents (topical CsA and corticosteroids, omega-3 fatty acids)
Tetracyclines
Plugs
Secretagogues
Serum
Contact lenses
Systemic immunosuppressives
Surgery (AMT, lid surgery, tarsorrhaphy, MM & SG transplant)

AMT = amniotic membrane transplantation; MM = mucous membrane; SG = salivary gland

eye treatment prior to formulating their treatment guidelines.^{184,185} The group favored the approach taken by the ITF, which based treatment recommendations on disease severity. A modification of the ITF severity grading scheme that contains 4 levels of disease severity based on signs and symptoms was formulated (Table 2). The subcommittee members chose treatments for each severity level from a menu of therapies for which evidence of therapeutic effect has been presented (Table 3). The treatment recommendations by severity level are presented in Table 4. It should be noted that these recommendations may be modified by practitioners based on individual patient profiles and clinical experience. The therapeutic recommendations for level 4 severity disease include surgical modalities to treat or prevent sight-threatening corneal complications. Discussion of these therapies is beyond the scope of this report.

V. UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

There have been tremendous advances in the treatment of dry eye and ocular surface disease in the last two decades, including FDA approval of cyclosporin emulsion as the first therapeutic agent for treatment of KCS in the United States. There has been a commensurate increase in knowledge regarding the pathophysiology of dry eye. This has led to a paradigm shift in dry eye management from simply lubricating and hydrating the ocular surface with artificial tears to strategies that stimulate natural production of tear constituents, maintain ocular surface epithelial health and barrier function, and inhibit the inflammatory factors that adversely impact the ability of ocular surface and glandular epithelia to produce tears. Preliminary experience using this new therapeutic approach suggests that quality of life can be improved for many patients with dry eye and that initiating these strategies early in the course of the disease may prevent potentially blinding complications of dry eye. It is likely that future therapies will focus on

Table 4. Treatment recommendations by severity level**Level 1:**

Education and environmental/dietary modifications
Elimination of offending systemic medications
Artificial tear substitutes, gels/ointments
Eye lid therapy

Level 2:

If Level 1 treatments are inadequate, add:
Anti-inflammatories
Tetracyclines (for meibomianitis, rosacea)
Punctal plugs
Secretagogues
Moisture chamber spectacles

Level 3:

If Level 2 treatments are inadequate, add:
Serum
Contact lenses
Permanent punctal occlusion

Level 4:

If Level 3 treatments are inadequate, add:
Systemic anti-inflammatory agents
Surgery (lid surgery, tarsorrhaphy; mucus membrane, salivary gland, amniotic membrane transplantation)

Modified from: International Task Force Guidelines for Dry Eye¹⁸⁵

replacing specific tear factors that have an essential role in maintaining ocular surface homeostasis or inhibiting key inflammatory mediators that cause death or dysfunction of tear secreting cells. This will require additional research to identify these key factors and better diagnostic tests to accurately measure their concentrations in minute tear fluid samples. Furthermore, certain disease parameters may be identified that will identify whether a patient has a high probability of responding to a particular therapy. Based on the progress that has been made and the number of therapies in the pipeline, the future of dry eye therapy seems bright.

REFERENCES

(Parenthetical codes following references indicate level of evidence, as described in Table 1. CS = Clinical Study; BS = Basic Science.)

- Gilbard JP, Rossi SR, Heyda KG. Ophthalmic solutions, the ocular surface, and a unique therapeutic artificial tear formulation. *Am J Ophthalmol* 1989;107:348-55 (**BS1**)
- Gilbard JP. Human tear film electrolyte concentrations in health and dry-eye disease. *Int Ophthalmol Clin* 1994;34:27-36 (**CS2**)
- Schein O, Tielsch J, Munoz B, et al. Relation between signs and symptoms of dry eye in the elderly. *Ophthalmology* 1997;104:1395-1400 (**CS2**)
- Nelson JD, Gordon JF. Topical fibronectin in the treatment of keratoconjunctivitis sicca. Chiron Keratoconjunctivitis Sicca Study Group. *Am J Ophthalmol* 1992;114:441-7 (**CS2**)
- Nelson JD. Impression cytology. *Cornea* 1988;7:71-81 (**BS1**)
- Ubels J, McCartney M, Lantz W, et al. Effects of preservative-free artificial tear solutions on corneal epithelial structure and function. *Arch Ophthalmol* 1995;113:371-8 (**BS1**)
- Green K, MacKeen DL, Slagle T, Cheeks L. Tear potassium contributes to maintenance of corneal thickness. *Ophthalmic Res* 1992;24:99-102 (**BS1**)

8. Holly F, Lemp M. Surface chemistry of the tear film: Implications for dry eye syndromes, contact lenses, and ophthalmic polymers. *Contact Lens Soc Am J* 1971;5:12-9 (BS2)
9. Perrigan DM, Morgan A, Quintero S, et al. Comparison of osmolarity values of selected ocular lubricants. ARVO 2004 poster session 449
10. Kaufman B, Novack GD. Compliance issues in manufacturing of drugs. *Ocul Surf* 2003;1:80-5
11. Albiets J, Bruce A. The conjunctival epithelium in dry eye subtypes: Effect of preserved and nonpreserved topical treatments. *Curr Eye Res* 2001;22:8-18 (CS2)
12. Gasset AR, Ishii Y, Kaufman H, Miller T. Cytotoxicity of ophthalmic preservatives. *Am J Ophthalmol* 1974;78:98-105 (BS1)
13. Wilson F. Adverse external effects of topical ophthalmic medications. *Surv Ophthalmol* 1979;24:57-88 (CS3)
14. Burstein N. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Surv Ophthalmol* 1980;25:15-30 (CS3)
15. Burstein N. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. *Trans Ophthalmol Soc UK*. 1985;104:402-9 (CS3)
16. Brubaker R, McLaren J. Uses of the fluorophotometer in glaucoma research. *Ophthalmology* 1985;92:884-90 (BS1)
17. Smith L, George M, Berdy G, Abelson M. Comparative effects of preservative free tear substitutes on the rabbit cornea: a scanning electron microscopic evaluation (ARVO abstract). *Invest Ophthalmol Vis Sci* 1991;32 (Suppl):733 (BS1)
18. Gilbard JP, Farris RL, Santamaria J 2nd. Osmolarity of tear microvolumes in keratoconjunctivitis sicca. *Arch Ophthalmol* 1978;96:677-81 (BS2)
19. Lopez Bernal D, Ubels JL. Quantitative evaluation of the corneal epithelial barrier: effect of artificial tears and preservatives. *Curr Eye Res* 1991;10:645-56 (BS1)
20. Bernal DL, Ubels JL. Artificial tear composition and promotion of recovery of the damaged corneal epithelium. *Cornea* 1993;12:115-20 (BS1)
21. Noecker R. Effects of common ophthalmic preservatives on ocular health. *Adv Ther* 2001;18:205-15 (CS1)
22. Tripathi BJ, Tripathi RC, Kolli SP. Cytotoxicity of ophthalmic preservatives on human corneal epithelium. *Lens Eye Toxicity Res* 1992;9:361-75 (BS1)
23. Herrema J, Friedenwald J. Retardation of wound healing in the corneal epithelium by lanolin. *Am J Ophthalmol* 1950;33:1421 (CS3)
24. Nelson J, Drake M, Brewer J, Tuley M. Evaluation of physiologic tear substitute in patients with keratoconjunctivitis sicca. *Adv Exp Med Biol* 1994;350:453-7 (CS2)
25. Gilbard JP, Rossi SR. An electrolyte-based solution that increases corneal glycogen and conjunctival goblet-cell density in a rabbit model for keratoconjunctivitis sicca. *Ophthalmology* 1992;99:600-4 (BS1)
26. Lenton LM, Albiets JM. Effect of carmellose-based artificial tears on the ocular surface in eyes after laser in situ keratomileusis. *J Refract Surg* 1999;15(2 Suppl):S227-S231 (CS2)
27. Slomiany BL, Slomiany A. Role of mucus in gastric mucosal protection. *J Physiol Pharmacol* 1991; 42:147-61 (BS1)
28. Gilbard JP. Tear film osmolarity and keratoconjunctivitis sicca. *CLAO J* 1985;11:243-50 (CS1)
29. Gilbard J. Tear film osmolarity and keratoconjunctivitis sicca. Lubbock TX, Dry Eye Institute, 1986 (CS3)
30. Gilbard J, Carter J, Sang D, et al. Morphologic effect of hyperosmolarity on rabbit corneal epithelium. *Ophthalmology* 1984;91:1205-12 (BS1)
31. Luo L, Li D, Corrales R, Pflugfelder S. Hyperosmolar saline is a proinflammatory stress on the mouse ocular surface. *Eye Contact Lens* 2005;31:186-93 (BS1)
32. Gilbard JP, Kenyon KR. Tear diluents in the treatment of keratoconjunctivitis sicca. *Ophthalmology* 1985;92:646-50 (CS2)
33. Holly F, Esquivel E. Colloid osmotic pressure of artificial tears. *J Ocul Pharmacol* 1985;1:327-36 (BS1)
34. Yancey PH. Organic osmolytes as compatible, metabolic and counteracting cryoprotectants in high osmolarity and other stresses. *J Exp Biol* 2005;208:2819-30 (BS2)
35. Holly F, Lemp M. Wettability and wetting of corneal epithelium. *Exp Eye Res* 1971;11:239-50 (BS1)
36. Hawi A, Smith T, Digenis G. A quantitative comparison of artificial tear clearance rates in humans using gamma scintigraphy (ARVO abstract). *Invest Ophthalmol Vis Sci* 1990;31 (Suppl):517 (BS1)
37. Argueso P, Tisdale A, Spurr-Michaud S, et al. Mucin characteristics of human corneal-limbal epithelial cells that exclude the rose bengal anionic dye. *Invest Ophthalmol Vis Sci* 2006;47:113-9 (BS1)
38. Versura P, Maltarello M, Stecher F, et al. Dry eye before and after therapy with hydroxypropylmethylcellulose. *Ophthalmologica* 1989;198:152-62 (CS3)
39. Simmons PA, Garrett Q, Xu S, et al. Interaction of carboxymethylcellulose with human corneal cells. ARVO 2006, E-Abstract 2759 (BS1)
40. Christiansen M, Cohen S, Rinehart J, et al. Clinical evaluation of an HP-guar gellable lubricant eye drop for the relief of dryness of the eye. *Curr Eye Res* 2004;28:55-62 (CS2)
41. Di Pascuale MA, Goto E, Tseng SC. Sequential changes of lipid tear film after the instillation of a single drop of a new emulsion eye drop in dry eye patients. *Ophthalmology* 2004;111:783-91 (CS2)
42. Korb DR, Scaffidi RC, Greiner JV, et al. The effect of two novel lubricant eye drops on tear film lipid layer thickness in subjects with dry eye symptoms. *Optom Vis Sci* 2005;82:594-601 (CS2)
43. Snibson GR, Greaves JL, Soper ND, et al. Precorneal residence times of sodium hyaluronate solutions studied by quantitative gamma scintigraphy. *Eye* 1990;4:594-602 (CS3)
44. Polack F, McNiece M. The treatment of dry eyes with NA hyaluronate (Healon). *Cornea* 1982;1:1333 (CS3)
45. Stuart JC, Linn JG. Dilute sodium hyaluronate (Healon) in the treatment of ocular surface disorders. *Ann Ophthalmol* 1985;17:190-2 (CS3)
46. DeLuise V, Peterson W. The use of topical Healon tears in the management of refractory dry-eye syndrome. *Ann Ophthalmol* 1984;16:823-4 (CS3)
47. Sand B, Marner K, Norm M. Sodium hyaluronate in the treatment of keratoconjunctivitis sicca. *Acta Ophthalmol* 1989; 67:181-3 (CS3)
48. Nelson JD, Farris RL. Sodium hyaluronate and polyvinyl alcohol artificial tear preparations a comparison in patients with keratoconjunctivitis sicca. *Arch Ophthalmol* 1988;106:484-7 (CS2)
49. Beetham WP. Filamentary keratitis. *Trans Am Ophthalmol Soc* 1936;33:413-35 (CS1)
50. Foulds WS. Intracanalicular gelatin implants in the treatment of keratoconjunctivitis sicca. *Br J Ophthalmol* 1961;45:625-7 (CS2)
51. Freeman JM. The punctum plug: evaluation of a new treatment for the dry eye. *Trans Am Acad Ophthalmol Otolaryngol* 1975;79:OP874-9 (CS2)
52. Tuberville AW, Frederick WR, Wood TO. Punctal occlusion in tear deficiency syndromes. *Ophthalmology* 1982;89:1170-2 (CS2)
53. Willis RM, Folberg R, Krachmer JH, et al. The treatment of aqueous-deficient dry eye with removable punctal plugs. A clinical and impression-cytological study. *Ophthalmology* 1987;94:514-8 (CS2)
54. Gilbard JP, Rossi SR, Azar DT, Gray KL. Effect of punctal occlusion by Freeman silicone plug insertion on tear osmolarity in dry eye disorders. *CLAO J* 1989;15:216-8 (CS2)
55. Balaram M, Schaumberg DA, Dana MR. Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome. *Am J Ophthalmol* 2001;131:30-6 (CS1)
56. Baxter SA, Laibson PR. Punctal plugs in the management of dry eyes. *Ocul Surf* 2004;2:255-65 (CS3)
57. Bartlett JD, Boan K, Corliss D, Gaddie IB. Efficacy of silicone punctal plugs as adjuncts to topical pharmacotherapy of glaucoma—a pilot study. Punctal Plugs in Glaucoma Study Group. *J Am Optom Assoc* 1996;67:664-8 (CS2)
58. Huang TC, Lee DA. Punctal occlusion and topical medications for glaucoma. *Am J Ophthalmol* 1989;107:151-5 (CS2)
59. Sugita J, Yokoi N, Fullwood NJ, et al. The detection of bacteria and bacterial biofilms in punctal plug holes. *Cornea* 2001;20: 362-5 (CS3)
60. Gerding H, Kupperts J, Busse H. Symptomatic cicatricial occlusion of canaliculi after insertion of Herrick lacrimal plugs. *Am J Ophthalmol* 2003;136:926-8 (CS3)
61. Lee J, Flanagan JC. Complications associated with silicone intracanalicular plugs. *Ophthal Plast Reconstr Surg* 2001;17:465-9 (CS3)
62. Paulsen F. The human lacrimal glands. *Adv Anat Embryol Cell Biol* 2003;170:III-XI,1-106 (BS1)
63. Yen MT, Pflugfelder SC, Feuer WJ. The effect of punctal occlusion on tear production, tear clearance, and ocular surface sensation in normal subjects. *Am J Ophthalmol* 2001;131:314-23 (CS2)
64. Tsubota K. The effect of wearing spectacles on the humidity of the eye. *Am J Ophthalmol* 1989;15:108:92-3 (BS2)
65. Tsubota K, Yamada M, Urayama K. Spectacle side panels and moist inserts for the treatment of dry-eye patients. *Cornea* 1994;13:197-201 (BS1)
66. Gresset J, Simonet P, Gordon D. Combination of a side shield with an ocular moisture chamber. *Am J Optom Physiol Opt* 1984;61:610-2 (CS3)
67. Savar DE. A new approach to ocular moisture chambers. *J Pediatr Ophthalmol Strabismus* 1978;15:51-3 (CS3)
68. Kurihashi K. Moisture aid during sleep for the treatment of dry eye: wet gauze eye mask. *Ophthalmologica* 1994;208:216-9 (CS3)
69. Nichols JJ, Ziegler C, Mitchell GL, Nichols KK. Self-reported dry eye dis-

- ease across refractive modalities. *Invest Ophthalmol Vis Sci* 2005;46:1911-4 (CS2)
70. Korb DR, Greiner JV, Glonek T, et al. Effect of periocular humidity on the tear film lipid layer. *Cornea* 1996;15:129-34 (BS2)
 71. Tsubota K, Hata S, Okusawa Y, et al. Quantitative videographic analysis of blinking in normal subjects and patients with dry eye. *Arch Ophthalmol* 1996;114:715-20 (BS1)
 72. Maruyama K, Yokoi N, Takamata A, Kinoshita S. Effect of environmental conditions on tear dynamics in soft contact lens wearers. *Invest Ophthalmol Vis Sci* 2004;45:2563-8 (BS1)
 73. Bacon AS, Astin C, Dart JK. Silicone rubber contact lenses for the compromised cornea. *Cornea* 1994;13:422-8 (CS3)
 74. Pullum KW, Whiting MA, Buckley RJ. Scleral contact lenses: the expanding role. *Cornea* 2005;24:269-77 (CS3)
 75. Tappin MJ, Pullum KW, Buckley RJ. Scleral contact lenses for overnight wear in the management of ocular surface disorders. *Eye* 2001;15(Pt 2):168-72 (CS3)
 76. Romero-Rangel T, Stavrou P, Cotter J, et al. Gas-permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol* 2000;130:25-32 (CS3)
 77. Rosenthal P, Cotter JM, Baum J. Treatment of persistent corneal epithelial defect with extended wear of a fluid-ventilated gas-permeable scleral contact lens. *Am J Ophthalmol* 2000;130:33-41 (CS3)
 78. Tauber J, Davitt WF, Bokosky JE, et al. Double-masked, placebo-controlled safety and efficacy trial of diquafosol tetrasodium (INS365) ophthalmic solution for the treatment of dry eye. *Cornea* 2004;23:784-92 (CS1)
 79. Mundasad MV, Novack GD, Allgood VE, et al. Ocular safety of INS365 ophthalmic solution: a P2Y(2) agonist in healthy subjects. *J Ocul Pharmacol Ther* 2001;17:173-9 (CS1)
 80. Murakami T, Fujihara T, Horibe Y, Nakamura M. Diquafosol elicits increases in net Cl⁻ transport through P2Y2 receptor stimulation in rabbit conjunctiva. *Ophthalmic Res* 2004;36:89-93 (BS1)
 81. Li DQ, Lokeshwar BL, Solomon A, et al. Regulation of MMP-9 in human corneal epithelial cells. *Exp Eye Res* 2001;73:449-59 (BS1)
 82. Murakami T, Fujita H, Fujihara T, et al. Novel noninvasive sensitive determination of tear volume changes in normal cats. *Ophthalmic Res* 2002;34:371-4 (BS1)
 83. Yerxa BR, Mundasad M, Sylvester RN, et al. Ocular safety of INS365 ophthalmic solution, a P2Y2 agonist, in patients with mild to moderate dry eye disease. *Adv Exp Med Biol* 2002;506(Pt B):1251-7 (BS2)
 84. Fujihara T, Murakami T, Fujita H, et al. Improvement of corneal barrier function by the P2Y(2) agonist INS365 in a rat dry eye model. *Invest Ophthalmol Vis Sci* 2001;42:96-100 (BS1)
 85. Fujihara T, Murakami T, Nagano T, et al. INS365 suppresses loss of corneal epithelial integrity by secretion of mucin-like glycoprotein in a rabbit short-term dry eye model. *J Ocul Pharmacol Ther* 2002;18:363-70 (BS1)
 86. Yerxa BR, Douglass JG, Elena PP, et al. Potency and duration of action of synthetic P2Y2 receptor agonists on Schirmer scores in rabbits. *Adv Exp Med Biol* 2002;506(Pt A):261-5 (BS2)
 87. Urashima H, Okamoto T, Takeji Y, et al. Rebamipide increases the amount of mucin-like substances on the conjunctiva and cornea in the N-acetylcysteine-treated in vivo model. *Cornea* 2004;23:613-9 (BS1)
 88. Taniito M, Takanashi T, Kaidzu S, et al. Cytoprotective effects of rebamipide and carteolol hydrochloride against ultraviolet B-induced corneal damage in mice. *Invest Ophthalmol Vis Sci* 2003;44:2980-5 (BS3)
 89. Masuda K, Tokushige H, Ogawa T, et al. Effect of topical ecabet sodium on mucin levels in the tear fluid of patients with dry eye. *SERI-ARVO* 2003.
 90. Toshida H, Nakata K, Hamano T, et al. Effect of gefarnate on the ocular surface in squirrel monkeys. *Cornea* 2002;21:292-9 (BS3)
 91. Nakamura M, Endo K, Nakata K, Hamano T. Gefarnate increases PAS positive cell density in rabbit conjunctiva. *Br J Ophthalmol* 1998;82:1320-3 (BS3)
 92. Nakamura M, Endo K, Nakata K, Hamano T. Gefarnate stimulates secretion of mucin-like glycoproteins by corneal epithelium in vitro and protects corneal epithelium from desiccation in vivo. *Exp Eye Res* 1997;65:569-74 (BS3)
 93. Toshida H, Nakata K, Hamano T, et al. Gefarnate stimulates goblet cell repopulation following an experimental wound to the tarsal conjunctiva in the dry eye rabbit. *Adv Exp Med Biol* 2002;506(Pt A):353-7 (BS 3)
 94. Hamano T. Dry eye treatment with eye drops that stimulate mucin production. *Adv Exp Med Biol* 1998;438:965-8 (CS3)
 95. Jumblatt JE, Cunningham L, Jumblatt MM. Effects of 15(S)-HETE on human conjunctival mucin secretion. *Adv Exp Med Biol* 2002;506(Pt A):323-7 (BS1)
 96. Gamache DA, Wei ZY, Weimer LK, et al. Corneal protection by the ocular mucin secretagogue 15(S)-HETE in a rabbit model of desiccation-induced corneal defect. *J Ocul Pharmacol Ther* 2002;18:349-61 (BS2)
 97. Jackson RS 2nd, Van Dyken SJ, McCartney MD, Ubels JL. The eicosanoid, 15-(S)-HETE, stimulates secretion of mucin-like glycoprotein by the corneal epithelium. *Cornea* 2001;20:516-21 (BS2)
 98. Azar RG, Edelhauser HE. Evaluation of the effects of 15(S)-HETE on corneal epithelial cells: an electrophysiological and cytochemical study. *Adv Exp Med Biol* 2002;506(Pt A):329-33 (BS3)
 99. Ubels JL, Aupperlee MD, Jackson RS 2nd, et al. Topically applied 15-(S)-HETE stimulates mucin production by corneal epithelium. *Adv Exp Med Biol* 2002;506(Pt A):317-21 (BS2)
 100. Gamache DA, Wei ZY, Weimer LK, et al. Preservation of corneal integrity by the mucin secretagogue 15(S)-HETE in a rabbit model of desiccation-induced dry eye. *Adv Exp Med Biol* 2002;506(Pt A):335-40 (BS2)
 101. Jumblatt JE, Cunningham LT, Li Y, Jumblatt MM. Characterization of human ocular mucin secretion mediated by 15(S)-HETE. *Cornea* 2002;21:818-24 (BS3)
 102. Vivino FB, Al-Hashimi I, Khan K, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjogren's syndrome. *Arch Intern Med* 1999;159:174-81 (CS1)
 103. Takaya M, Ichikawa Y, Yamada C, et al. Treatment with pilocarpine hydrochloride for sicca symptoms in Sjogren's syndrome. *Ryumachi* 1997;37:453-7 (CS2)
 104. Tsifetaki N, Kitsos G, Paschides CA, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjogren's syndrome: a randomised 12-week controlled study. *Ann Rheum Dis* 2003;62:1204-7 (CS2)
 105. Papas AS, Sherrer YS, Charney M, et al. Successful treatment of dry mouth and dry eye symptoms in Sjogren's syndrome patients with oral pilocarpine: A randomized, placebo-controlled, dose-adjustment study. *J Clin Rheumatol* 2004;4:169-77 (CS1)
 106. Aragona P, Di Pietro R, Spinella R, Moberici M. Conjunctival epithelium improvement after systemic pilocarpine in patients with Sjogren's syndrome. *Br J Ophthalmol* 2006;90:166-70 (CS2)
 107. Petrone D, Condemi JJ, Fife R, et al. Double-blind randomized placebo-controlled study of cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum* 2002;46:748-54 (CS1)
 108. Ono M, Takamura E, Shinozaki K, et al. Therapeutic effect of cevimeline on dry eye in patients with Sjogren's syndrome: a randomized, double-blind clinical study. *Am J Ophthalmol* 2004;138:6-17 (CS1)
 109. Geerling G, Daniels JT, Dart JK, et al. Toxicity of natural tear substitutes in a fully defined culture model of human corneal epithelial cells. *Invest Ophthalmol Vis Sci* 2001;42:948-56 (BS1)
 110. Geerling G, Honnicke K, Schroder C, et al. Quality of salivary tears following autologous submandibular gland transplantation for severe dry eye. *Graefes Arch Clin Exp Ophthalmol* 2000;238:45-52 (BS1)
 111. Tsubota K, Goto E, Fujita H, et al. Treatment of dry eye by autologous serum application in Sjogren's syndrome. *Br J Ophthalmol* 1999;83:390-5 (CS2)
 112. Geerling G, Hartwig D. Autologous serum eyedrops for ocular surface disorders, in Reinhard T, Larkin F (eds). *Cornea and external eye disease*. Berlin, Heidelberg, Springer, 2005, pp 2-19
 113. Liu L, Hartwig D, Harloff S, et al. An optimised protocol for the production of autologous serum eyedrops. *Graefes Arch Clin Exp Ophthalmol* 2005;243:706-14 (BS1)
 114. Tananuvat, N, Daniell M, Sullivan LJ, et al. Controlled study of the use of autologous serum in dry eye patients. *Cornea* 2001;20:802-6 (CS1)
 115. Kojima T, Ishida R, Dogru M, et al. The effect of autologous serum eyedrops in the treatment of severe dry eye disease: a prospective randomized case-control study. *Am J Ophthalmol* 2005;139:242-6 (CS1)
 116. Noble BA, Loh RS, MacLennan S, et al. Comparison of autologous serum eye drops with conventional therapy in a randomised controlled crossover trial for ocular surface disease. *Br J Ophthalmol* 2004;88:647-52 (CS1)
 117. Noda-Tsuruya T, Asano-Kato N, Toda I, Tsubota K. Autologous serum eye drops for dry eye after LASIK. *J Refract Surg* 2006;22:61-6 (CS1)
 118. Schulze SD, Sekundo W, Kroll P. Autologous serum for the treatment of corneal epithelial abrasions in diabetic patients undergoing vitrectomy. *Am J Ophthalmol* 2006;142:207-11 (BS1)
 119. Geerling G, Sieg P, Bastian GO, Laqua H. Transplantation of the autologous submandibular gland for most severe cases of keratoconjunctivitis sicca. *Ophthalmology* 1998;105:327-35 (CS2)
 120. Schroder, Sieg P, Framme C, et al. [Transplantation of the submandibular gland in absolute dry eyes. Effect on the ocular surface]. *Klin Monatsbl Augenheilkd* 2002;219:494-501 (CS2)
 121. Luo L, Li DQ, Doshi A, et al. Experimental dry eye stimulates production

- of inflammatory cytokines and MMP-9 and activates MAPK signaling pathways on the ocular surface. *Invest Ophthalmol Vis Sci* 2004;45:4293-301 (BS1)
122. Niederhorn JY, Stern ME, Pflugfelder SC, et al. Desiccating stress induces T cell-mediated Sjogren's syndrome-like lacrimal keratoconjunctivitis. *J Immunol* 2006;176:3950-7 (BS1)
 123. Kaswan RL, Salisbury MA, Ward DA. Spontaneous canine keratoconjunctivitis sicca. A useful model for human keratoconjunctivitis sicca: treatment with cyclosporine eye drops. *Arch Ophthalmol* 1989;107:1210-16 (BS2)
 124. Gunduz K, Ozdemir O. Topical cyclosporin treatment of keratoconjunctivitis sicca in secondary Sjogren's syndrome. *Acta Ophthalmol* 1994;72:38-42 (CS2)
 125. Laibovitz RA, Solch S, Andrianao J. Pilot trial of cyclosporin 1% ophthalmic ointment in the treatment of keratoconjunctivitis sicca. *Cornea* 1993;12:315-23 (CS1)
 126. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease. A dose-ranging, randomized trial. *Ophthalmology* 2000;107:967-74 (CS1)
 127. 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. *Ophthalmology* 2000;107:631-9 (CS1)
 128. Kunert KS, Tisdale AS, Gipson IK. Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. *Arch Ophthalmol* 2002;120:330-7 (BS1)
 129. Brignole F, Pisella PJ, De Saint Jean M, et al. Flow cytometric analysis of inflammatory markers in KCS: 6-month treatment with topical cyclosporin A. *Invest Ophthalmol Vis Sci* 2001;42:90-5 (BS1)
 130. Turner K, Pflugfelder SC, Ji Z, et al. Interleukin-6 levels in the conjunctival epithelium of patients with dry eye disease treated with cyclosporine ophthalmic emulsion. *Cornea* 2000;19:492-6 (BS1)
 131. Kunert KS, Tisdale AS, Stern ME, Smith JA. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. *Arch Ophthalmol* 2000;118:1489-96 (BS1)
 132. Pflugfelder SC, Maskin SL, Anderson B, et al. A randomized, double-masked, placebo-controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5%, and placebo for treatment of keratoconjunctivitis sicca in patients with delayed tear clearance. *Am J Ophthalmol* 2004;138:444-57 (CS1)
 133. Avunduk AM, Avunduk MC, Varnell ED, Kaufman HE. The comparison of efficacies of topical corticosteroids and nonsteroidal antiinflammatory drops on dry eye patients: A clinical and immunocytochemical study. *Am J Ophthalmol* 2003;136:593-602 (CS1)
 134. Sainz de la Maza Serra SM, Simon Castellvi C, Kabbani O. Nonpreserved topical steroids and punctal occlusion for severe keratoconjunctivitis sicca. *Arch Soc Esp Oftalmol* 2000;75:751-56 (CS1)
 135. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome. *Ophthalmology* 1999;106:811-6 (CS3)
 136. Pflugfelder SC. Antiinflammatory therapy for dry eye. *Am J Ophthalmol* 2004;137:337-42 (CS3)
 137. Anonymous. Certain ophthalmic antibiotic combination drugs for human use; Drug efficacy study implementation. *Fed Reg* 1982;47:21296
 138. Anonymous. Certain steroid preparations for ophthalmic and/or otic use. *Fed Reg* 1980a;45:57776-80
 139. Anonymous. Certain ophthalmic antibiotic combination drugs for human use; Drug efficacy study implementation. *Fed Reg* 1980b;45:57780-3
 140. Anonymous. Certain steroid preparations for ophthalmic or otic use. *Fed Reg* 1976;41:34340-2
 141. De Paiva CS, Corrales RM, Villarreal AL, et al. Apical corneal barrier disruption in experimental murine dry eye is abrogated by methylprednisolone and doxycycline. *Invest Ophthalmol Vis Sci* 2006;47:2847-56 (RS1)
 142. De Paiva CS, Corrales RM, Villarreal AL, 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;83:526-35 (RS1)
 143. Schiffman RM, Bradford R, Bunnell B, et al. A multicenter, double-masked, randomized, vehicle-controlled, parallel-group study to evaluate the safety and efficacy of testosterone ophthalmic solution in patients with meibomian gland dysfunction. ARVO 2006, E-Abstract 5608 (CS3)
 144. Worda C, Nepp J, Huber JC, Sator MO. Treatment of keratoconjunctivitis sicca with topical androgen. *Maturitas* 2001;37:209-12 (CS3)
 145. Sator MO, Joura EA, Golaszewski T, et al. Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol. *Br J Obstet Gynaecol* 1998;105:100-2 (CS2)
 146. Shine WE, McCulley JP, Pandya AG. Minocycline effect on meibomian gland lipids in meibomianitis patients. *Exp Eye Res* 2003;76:417-20 (CS2)
 147. Dougherty JM, McCulley JP, Silvany RE, et al. The role of tetracycline in chronic blepharitis. *Invest Ophthalmol Vis Sci* 1991;32:2970-5 (CS2)
 148. Ta CN, Shine WE, McCulley JP, et al. Effects of minocycline on the ocular flora of patients with acne rosacea or seborrheic blepharitis. *Cornea* 2003;22:545-8 (CS2)
 149. Solomon A, Rosenblatt M, Li DQ, et al. Doxycycline inhibition of interleukin-1 in the corneal epithelium. *Invest Ophthalmol Vis Sci* 2000;41:2544-57 (CS2)
 150. Li Y, Kuang K, Yersa B, et al. Rabbit conjunctival epithelium transports fluid, and P2Y2(2) receptor agonists stimulate Cl(-) and fluid secretion. *Am J Physiol Cell Physiol* 2001;281:C595-602 (BS1)
 151. Li DQ, Luo L, Chen Z, et al. JNK and ERK MAP kinases mediate induction of IL-1beta, TNF-alpha and IL-8 following hyperosmolar stress in human limbal epithelial cells. *Exp Eye Res* 2006;82:588-96. Epub 2005 Oct 3 (BS1)
 152. Krakauer T, Buckley M. Doxycycline is anti-inflammatory and inhibits staphylococcal exotoxin-induced cytokines and chemokines. *Antimicrob Agents Chemother* 2003;47:3630-3 (BS1)
 153. Voils SA, Evans ME, Lane MT, et al. Use of macrolides and tetracyclines for chronic inflammatory diseases. *Ann Pharmacother* 2005;39:86-94 (CS3)
 154. Tamargo RJ, Bok RA, Brem H. Angiogenesis inhibition by minocycline. *Cancer Res* 1991;51:672-5 (BS1)
 155. Sapadin AN, Fleischmajer R. Tetracyclines: Nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006;54:258-65 (CS3)
 156. Habif TP. Clinical dermatology, 4th ed. St Louis: Mosby-Year Book, 2004, pp 162-89 (CS3)
 157. Velicer CM, Heckbert SR, Lampe JW, et al. Antibiotic use in relation to the risk of breast cancer. *JAMA* 2004;291:827-35
 158. Velicer CM, Heckbert SR, Rutter C, et al. Association between antibiotic use prior to breast cancer diagnosis and breast tumour characteristics (United States). *Cancer Causes Control (Netherlands)* 2006;17:307-13
 159. Garcia Rodriguez LA, Gonzalez-Perez A. Use of antibiotics and risk of breast cancer. *Am J Epidemiology* 2005;161:616-9
 160. Macdonald A, Feiwel M. Perioral dermatitis: aetiology and treatment with tetracycline. *Br J Dermatol* 1972;87:315-9 (CS3)
 161. Jansen T, Plewig G. Rosacea: classification and treatment. *J R Soc Med* 1997;90:144-50 (CS3)
 162. Frucht-Pery J, Chayet AS, Feldman ST, et al. The effect of doxycycline on ocular rosacea. *Am J Ophthalmol* 1989;107:434-5 (CS2)
 163. Wilkin JK. Rosacea. pathophysiology and treatment. *Arch Dermatol* 1994;130:359-62 (BS1)
 164. Stone DU, Chodosh J. Oral tetracyclines for ocular rosacea: an evidence-based review of the literature. *Cornea* 2004;23:106-9 (CS1)
 165. McCulley JP, Dougherty JM, Deneau DG. Classification of chronic blepharitis. *Ophthalmology* 1982;89:1173-80 (CS2)
 166. Frucht-Pery J, Sagi E, Hemo I, Ever-Hadani P. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993;116:88-92 (CS1)
 167. Seal DV, Wright P, Picker L, et al. Placebo controlled trial of fusidic acid gel and oxytetracycline for recurrent blepharitis and rosacea. *Br J Ophthalmol* 1995;79:42-5 (CS1)
 168. Hoeprich PD, Warshauer DM. Entry of four tetracyclines into saliva and tears. *Antimicrob Agents Chemother* 1974;3:330-6 (BS1)
 169. Gullbenkian A, Myers J, Freis D. Hamster flank organ hydrolase and lipase activity. *J Invest Dermatol* 1980;75:289-92 (BS1)
 170. Aronowicz JD, Shine WE, Oral D, et al. Short term oral minocycline treatment of meibomianitis. *Br J Ophthalmol* 2006;90:856-60 (CS2)
 171. Yoo SE, Lee DC, Chang MH. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. *Korean J Ophthalmol* 2005;19:258-63 (CS2)
 172. Browning DJ, Proia AD. Ocular rosacea. *Surv Ophthalmol* 1986;31:145-58 (CS3)
 173. Esterly NB, Koransky JS, Furey NL, et al. Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy. *Arch Dermatol* 1984;120:1308-13 (BS1)
 174. Gilbard JP. The scientific context and basis of the pharmacologic management of dry eyes. *Ophthalmol Clin North Am* 2005;18:475-84, v (CS3)
 175. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000;71(1 Suppl):343S-8S (BS2)
 176. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med*

- 1989;320:265-71 **(BS1)**
177. James MJ, Cleland LG. Dietary n-3 fatty acids and therapy for rheumatoid arthritis. *Semin Arthritis Rheum* 1997;27:85-97 **(CS3)**
178. Kremer JM. n-3 fatty acid supplements in rheumatoid arthritis. *Am J Clin Nutr* 2000;71(1 Suppl):349S-51S **(CS1)**
179. Barabino S, Rolando M, Camicione P, et al. Systemic linoleic and gamma-linolenic acid therapy in dry eye syndrome with an inflammatory component. *Cornea* 2003;22:97-101 **(CS2)**
180. Seedor JA, Lamberts D, Bergmann RB, Perry HD. Filamentary keratitis associated with diphenhydramine hydrochloride (Benadryl). *Am J Ophthalmol* 1986;101:376-7 **(CS3)**
181. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol* 2000;118:1264-68
182. Mader TH, Stulting RD. Keratoconjunctivitis sicca caused by diphenoxylate hydrochloride with atropine sulfate (Lomotil). *Am J Ophthalmol* 1991;111:377-8 **(CS2)**
183. Tsubota K, Nakamori K. Dry eyes and video display terminals. *N Engl J Med* 1993;25:328:584 **(CS2)**
184. Matoba AY, Harris DJ, Mark DB, et al. Dry eye syndrome, American Academy of Ophthalmology, 2003
185. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: A Delphi approach to treatment recommendations. *Cornea* 2006;25:900-7