PREFERRED PRACTICE PATTERN®

Dry Eye Syndrome

AMERICAN ACADEMY® OF OPHTHALMOLOGY
The Eye M.D. Association

Approved by: Board of Trustees
September 21, 2013

This document should be cited as follows:
American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp.

Preferred Practice Pattern® guidelines are developed by the Academy's H. Dunbar Hoskins Jr., MD Center for Quality Eye Care without any external financial support. Authors and reviewers of the guidelines are volunteers and do not receive any financial compensation for their contributions to the documents. The guidelines are externally reviewed by experts and stakeholders before publication.

CORNEA/EXTERNAL DISEASE PREFERRED PRACTICE PATTERN DEVELOPMENT PROCESS AND PARTICIPANTS

The **Cornea/External Disease Preferred Practice Pattern® Panel** members wrote the Dry Eye Syndrome Preferred Practice Pattern® guidelines ("PPP"). The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in March 2013. The document was edited in response to the discussion and comments.

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The Dry Eye Syndrome PPP was then sent for review to additional internal and external groups and individuals in June 2013. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered. Members of the Cornea/External Disease Preferred Practice Pattern Panel reviewed and discussed these comments and determined revisions to the document.

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FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at www.cmss.org/codeforinteractions.aspx), relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at http://one.aao.org/CE/PracticeGuidelines/PPP.aspx). A majority (70%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2012–2013 had no financial relationship to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to August 2013 are available online at www.aao.org/ppp.

TABLE OF CONTENTS

OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that **identify characteristics and components of quality eye care.** Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern® guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern® guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved U.S. Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern® guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the "approved by" date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at http://one.aao.org/CE/PracticeGuidelines/PPP.aspx) to comply with the Code.

The intended users of the Dry Eye Syndrome PPP are ophthalmologists.

METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2]as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points determined by the PPP panel to be of particular importance to vision and quality of life outcomes.
- All recommendations for care in this PPP were rated using the system described above. To locate ratings for specific recommendations, see Appendix 2 for additional information.
- Literature searches to update the PPP were undertaken in June 2012 and January 2013 in PubMed and the Cochrane Library. Complete details of the literature search are available at www.aao.org/ppp.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

Dry eye is a common ocular condition that has a high impact on the quality of life of afflicted individuals owing to discomfort or visual disability. Although the symptoms improve with treatment, the condition is usually not curable. Dry eye can be a cause of visual disability and may compromise results of corneal, cataract, and refractive surgery.

No single test is adequate for establishing the diagnosis of dry eye. The constellation of findings from multiple tests can add greatly to the clinician's understanding of the patient's condition. Evaluation of conjunctival staining is helpful but underutilized.

About 10% of patients with clinically significant aqueous deficient dry eye have an underlying primary Sjögren syndrome. Patients with moderate punctate staining of the cornea and/or conjunctiva should be considered for testing for an underlying Sjögren syndrome, as these patients will require a multidisciplinary approach.

Pharmacological and procedural treatments are associated with improvements in patient symptoms and clinical signs, although chronic therapy and patient compliance are necessary for long-term management.

Punctal plugs may be helpful in moderate to severe cases of aqueous deficient dry eye. However, patients treated with punctal plugs should be monitored regularly to ensure that the plugs are present and in the proper position.

Omega-3 fatty acid products without ethyl esters may be beneficial in the treatment of dry eye, though the evidence is insufficient to establish the effectiveness of any particular formulation and may increase the risk of prostate cancer.

Cyclosporine treatment has been shown to have short-term clinical benefits in the treatment of dry eye. However, insofar as dry eye is a life-long condition whose symptoms and signs wax and wane, cost considerations and the lack of data on long-term effectiveness are important factors in the decision to prescribe cyclosporine. It is also unclear whether the estimated benefit is observed in all patient subpopulations.

Dry eye patients considering keratorefractive surgery, particularly LASIK, should be cautioned that the dry eye condition could become worse after surgery. Dry eye symptoms are common in the first few months after surgery and tend to subside with time. Patients can safely undergo LASIK surgery if a pre-existing dry eye condition can be controlled preoperatively.

Patients with severe dry eye are at greater risk for contact lens intolerance and associated complications. Patients with pre-existing dry eye should be cautioned that keratorefractive surgery, particularly LASIK, may worsen their dry eye condition.

INTRODUCTION

DISEASE DEFINITION

Dry eye syndrome (ICD-9 #375.15; ICD-10 #H04.12- [(–) = 1, right eye; 2, left eye; 3, bilateral])

For the purpose of this PPP, dry eye syndrome refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation, associated with ocular discomfort and/or visual symptoms and possible disease of the ocular surface.

PATIENT POPULATION

The patient population includes individuals of all ages who present with symptoms and signs suggestive of dry eye, such as ocular irritation, redness, mucous discharge, fluctuating vision, and decreased tear meniscus or break-up time.

CLINICAL OBJECTIVES

- Establish the diagnosis of dry eye and differentiate it from other causes of irritation and redness that may complicate both patient care and research on tear deficiency
- Identify the local and systemic causes of dry eye syndrome
- Establish appropriate therapy
- Relieve discomfort
- Prevent worsening of symptoms and clinical findings
- Educate and involve the patient in the management of this disease

BACKGROUND

Dry eye, either alone or in combination with other conditions, is a frequent cause of ocular irritation that leads patients to seek ophthalmologic care.[4] While these symptoms often improve with treatment, the disease usually is not curable, which may be a source of patient and physician frustration. Dry eye can be a cause of visual morbidity and may compromise results of corneal, cataract, and refractive surgery.

PREVALENCE AND RISK FACTORS

Epidemiological information on dry eye syndrome has been limited by lack of uniformity in its definition and the inability of any single diagnostic test or set of diagnostic tests to confirm or rule out the condition. Dry eye syndrome is a common condition that causes varying degrees of discomfort and disability. While clinic-based studies confirm its frequency (17% of 2127 consecutive new outpatients were diagnosed with dry eye following comprehensive examination), such studies may not reflect the overall population.[5] In a population-based sample of 2520 elderly (65 or older) residents of Salisbury, Maryland, 14.6% were symptomatic, which was defined as reporting one or more dry eye symptoms often or all the time.[4] The combination of being symptomatic and having a low Schirmer test (≤5 mm with anesthesia) or a high rose bengal score (≥5) was seen in 3.5% of the residents.[4] Depending on which of these two percentages is used, extrapolating to the U.S. population aged 65 to 84 yields estimates of approximately 1 million to 4.3 million people who have dry eye. A population-based study of dry eye conducted in Melbourne, Australia, using different diagnostic criteria reported higher percentages of the 926 participants aged 40 to 97 who had a low Schirmer test (16.3% ≤8 mm) or a high rose bengal score (10.8% ≥4).[6] The prevalence of self-reported dry eye in 3722 participants of the Beaver Dam (Wisconsin) Eye Study varied from 8.4% of subjects younger than 60 to 19.0% of those over 80, with an overall prevalence of 14.4%.[7] The Men's Health Study revealed that the prevalence of dry eye disease in men increased from 3.90% to 7.67% when men aged 50 to 54 were compared with men over 80 (n = 25,444). Dry eye was defined as a reported clinical diagnosis or symptoms of both dryness and irritation either constantly or often.[8] In a similar Women's Health Study of over 39,000 women, the prevalence of dry eye was 5.7% among women younger than 50 and increased to 9.8% among women over 75. This was a survey in which dry eye was defined as above.[9] In a clinic setting, the proportion of 224 subjects identified with dry eye were far more likely to

exhibit signs of evaporative dry eye resulting from meibomian gland disfunction (MGD) than from pure aqueous deficient dry eye.[10]

Estimates of dry eye prevalence based on treatment-derived data yield much lower percentages. A study evaluating medical claims data for nearly 10 million enrollees in managed care plans found that dry eye was diagnosed or treated with punctal occlusion in 0.4% to 0.5% of the enrollees.[8,9,11]

Many risk factors for dry eye have been proposed (see Table 1). Older age and female gender have been identified as risk factors for dry eye.[6,7,11-14] A Japanese study found an increased prevalence of dry eye disease among Japanese office workers using visual display terminals.[15] Concurrent use of benzalkonium chloride (BAK)-containing glaucoma medications was also shown to be a risk factor in glaucoma patients.[16,17] Arthritis was evaluated as a risk factor in two studies and found to be associated with an increased risk of dry eye in both.[6,7] The Beaver Dam Eye Study found that after controlling for age and gender, smoking, and multivitamin use were associated with an increased risk of dry eye, whereas caffeine use was associated with a decreased risk.[7] An update to the Beaver Dam Study[14] found that additional risk factors for dry eye included the use of antihistamines, antidepressant and antianxiety medications, and oral corticosteroids. Angiotensin-converting enzyme inhibitors were associated with a lower risk. Within the 25,665 postmenopausal women in the Women's Health Study, hormone replacement therapy, and, in particular, estrogen use alone, was associated with an increased risk of clinically diagnosed dry eye syndrome or severe symptoms.[18] More recent reports have suggested a relationship between botulinum toxin injection and dry eye.[19-21]

A study of dry eye and quality of life found decreased quality of life for all severity levels of dry eye syndrome, with an effect on quality of life for severe dry eye comparable with that reported for moderate angina.[22] One study of a cohort of dry eye patients found a strong association with anxiety and depression.[23] Several other studies demonstrated a relationship between depression and dry eye symptoms (with or without dry eye signs) independent of the medications used to treat depression.[24,25] Other research suggests that patients with dry eye are more likely to report pain, limitations of activities of daily living, and lower quality of life.[17,26,27]

TABLE 1 RISK FACTORS FOR DRY EYE

Level of Evidence		
Mostly Consistent*	Suggestive†	Unclear‡
• Older age	• Asian ethnicity	• Cigarette smoking
• Female gender	• Medications	• Hispanic ethnicity
• Postmenopausal estrogen therapy	◦ Tricyclic antidepressants	• Medications
• Low dietary intake of omega-3 fatty acids	◦ Selective serotonin reuptake inhibitors	◦ Anticholinergics
• Medications	◦ Diuretics	◦ Anxiolytics
◦ Antihistamines	◦ Beta-blockers	◦ Antipsychotics
• Connective-tissue disease	• Diabetes mellitus	• Alcohol use
• LASIK and refractive excimer laser surgery	• HIV/HTLV1 infection	• Menopause
• Radiation therapy	• Systemic chemotherapy	• Botulinum toxin injection
• Hematopoietic stem cell transplantation	• Large-incision ECCE and penetrating keratoplasty	• Acne
• Vitamin A deficiency	• Isotretinoin	• Gout
• Hepatitis C infection	• Low-humidity environments	• Oral contraceptives
• Androgen deficiency	• Sarcoidosis	• Pregnancy
	• Ovarian dysfunction	

Reproduced with permission from Smith JA (Chair). Epidemiology Subcommittee of the International Dry Eye Workshop. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007). Ocul Surf 2007;5:99.

ECCE = extracapsular cataract extraction; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus

* Mostly consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data.

† Suggestive evidence implies the existence of either 1) inconclusive information from peer-reviewed publication or 2) inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal.

‡ Unclear evidence implies either directly conflicting information in peer-reviewed publications or inconclusive information but with some basis for a biological rationale.

PATHOGENESIS

The ocular surface and tear-secreting glands function as an integrated unit.[28] Disease or dysfunction of this functional unit results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and possible damage to the ocular surface epithelium. Dysfunction of this integrated unit may develop from aging, a decrease in supportive factors (such as androgen hormones), systemic inflammatory diseases (such as Sjögren syndrome or rheumatoid arthritis), ocular surface diseases (such as herpes simplex virus [HSV] keratitis) or surgeries that disrupt the trigeminal afferent sensory nerves (e.g., LASIK), and systemic diseases or medications that disrupt the efferent cholinergic nerves that stimulate tear secretion.[29] Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface that involves both soluble and cellular mediators.[30,31] Clinical and basic research suggests that this inflammation plays a role in the pathogenesis of dry eye (see Figure 1).[32,33]

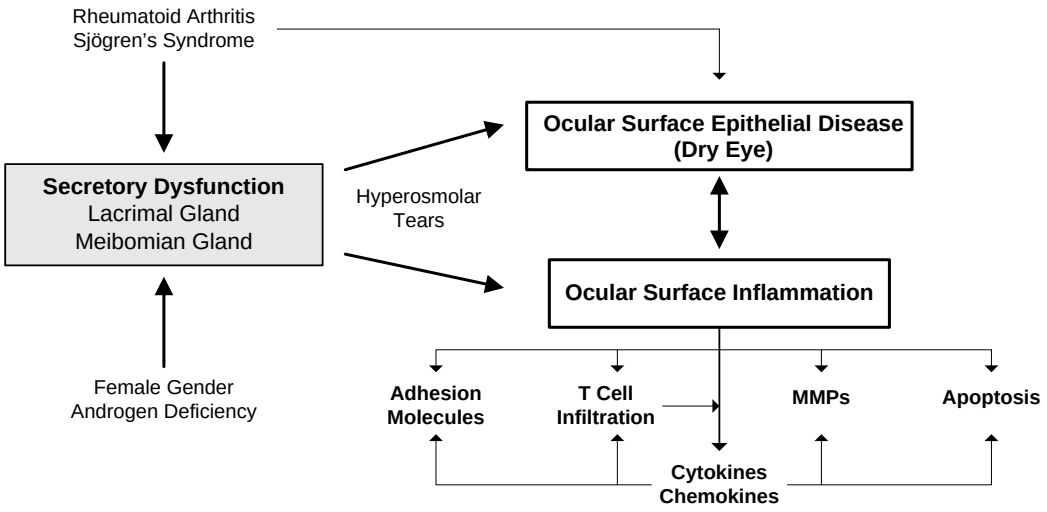

FIGURE 1. INFLAMMATORY MEDIATORS IN DRY EYE

Modified from Pflugfelder SC. Antiinflammatory therapy for dry eye. Am J Ophthalmol 2004;137:338, with permission from Elsevier.

MMPs = matrix metalloproteinases

ASSOCIATED CONDITIONS

Symptoms caused by dry eye may be exacerbated by the use of systemic medications such as diuretics, antihistamines, anticholinergics, antidepressants, and systemic retinoids (e.g., isotretinoin).[7,8,14,16,34-37] Instillation of any eye medications, especially when they are instilled frequently (e.g., more than four drops a day), may prevent the normal maintenance of the tear film and cause dry eye symptoms. In addition, environmental factors, such as reduced humidity and increased wind, drafts, air conditioning, or heating may exacerbate the ocular discomfort of patients with dry eye. Exogenous irritants and allergens, although not believed to be causative of dry eye, may exacerbate the symptoms.

Hyposecretory MGD may be a precursor to obstructive MGD and may play a role in the pathogenesis of dry eye disease.[38]

Rosacea is a disease of the skin and eye that is observed more frequently in fair-skinned individuals,[39] but it can occur in people of all racial origins. Characteristic facial skin findings include erythema, telangiectasia, papules, pustules, prominent sebaceous glands, and rhinophyma. Rosacea may be difficult to diagnose in patients with darker skin tones because of the difficulty in visualizing telangiectasia or facial flushing.[39] While rosacea is more prevalent in women, it can be more severe when it occurs in men.[40,41] Because many patients exhibit only mild signs, such as telangiectasia and a history of easy facial flushing, the diagnosis of rosacea is often overlooked, especially in children who may present with chronic recurrent blepharokeratoconjunctivitis, punctate erosions, peripheral

keratitis, MGD, or recurrent chalazia and have subtle signs of rosacea.[42] Children with ocular rosacea often present with corneal involvement and asymmetry of ocular disease, and the potential for sight-threatening visual impairment should be considered. Cutaneous rosacea is less frequent in children and associated atopy is common.[43,44] Children with a history of styes have an increased risk of developing adult rosacea.[45]

When there is an associated systemic disease such as Sjögren syndrome, an inflammatory cellular infiltration of the exocrine glands (including lacrimal gland) leads to saliva- and tear-production deficiency (see Appendix 3). About 10% of patients with clinically significant aqueous deficient dry eye have an underlying primary Sjögren syndrome.[46,47] Primary Sjögren syndrome is a multisystem disorder with systemic involvement and increased risk of lymphoma.[48] About 5% of patients with Sjögren syndrome will develop some form of lymphoid malignancy.[49] A recent meta-analysis found that among rheumatic diseases, primary Sjögren syndrome is the most strongly associated risk factor for malignancy, with an incidence rate of 18.9 (95% CI = 9.4–37.9), implying an increased incidence of 320 cases per 100,000 patient-years.[50] Therefore, ophthalmologists caring for patients with clinically significant dry eye should have a high index of suspicion for Sjögren syndrome and a low threshold for serological work-up for diagnostic purposes.

Aqueous tear deficiency may develop in other systemic conditions that result in infiltration of the lacrimal gland and replacement of the secretory acini such as lymphoma, sarcoidosis,[51,52] hemochromatosis, and amyloidosis.[53] Dry eye may develop in patients with systemic viral infections; it has been reported in patients infected by the retroviruses, human T-cell lymphotropic virus type 1, and human immunodeficiency virus (HIV).[54] Dry eye was diagnosed in 21% of a group of patients with AIDS,[55] and a condition known as diffuse infiltrative lymphadenopathy syndrome has been reported in patients with HIV infection, most of whom were children.[54] Decreased tear secretion and reduced tear concentrations of lactoferrin have been reported in patients with hepatitis C.[56,57] Lacrimal gland swelling, dry eye, and Sjögren syndrome have been associated with primary and persistent Epstein-Barr virus infections.[58-61] Severe dry eye has been reported in recipients of hematopoietic stem cell transplants with or without the development of graft-versus-host disease (GVHD).[62,63] In chronic GVHD, there is infiltration and fibrosis of the lacrimal glands and conjunctiva as a result of T-cell interaction with fibroblasts.[62,64,65] Diseases such as ocular mucous membrane pemphigoid and Stevens-Johnson syndrome produce tear deficiency due to inflammation, scarring, and destruction of the conjunctival goblet cells. Atopy may produce dry eye that results from blepharitis, conjunctival scarring, or antihistamine use. More generally, as dry eye is known to be most common in post-menopausal women, younger patients and males should be viewed with suspicion of systemic or local associated conditions.

Eyelid conditions associated with dry eye include eyelid malposition, lagophthalmos, and blepharitis as well as neuromuscular disorders that affect blinking (e.g., Parkinson disease, Bell palsy).[66] Orbital surgery, radiation, and injury may also lead to dry eye.

NATURAL HISTORY

Dry eye syndrome varies in severity, duration, and etiology.[67] In the majority of patients, the condition is not sight-threatening and is characterized by intermittently blurred vision and troublesome symptoms of irritation that are usually worse at the end of the day. In some individuals, exacerbating factors such as systemic medications that decrease tear production or environmental conditions that increase tear evaporation may lead to an acute increase in the severity of symptoms. Elimination of such factors often leads to marked improvement and may even be curative. The disease may exhibit chronicity, characterized by fluctuating severity of symptoms and/or a gradual increase in symptom severity with time.

Reversible conjunctival squamous metaplasia and punctate epithelial erosions of the conjunctiva and cornea develop in many patients who have clinically significant dry eye. Rarely, patients with severe dry eye will develop complications such as ocular surface keratinization; corneal scarring, thinning, or neovascularization; microbial or sterile corneal ulceration with possible perforation; and severe visual loss.[68]

CARE PROCESS

PATIENT OUTCOME CRITERIA

Outcome criteria for treating dry eye include the following:

- Reduce or alleviate signs and symptoms of dry eye, such as ocular irritation, redness, or mucous discharge
- Maintain and improve visual function
- Reduce or prevent structural damage

DIAGNOSIS

Many ocular surface diseases produce symptoms that are similar to those associated with dry eye, including foreign body sensation, mild itching, irritation, and soreness. Identifying characteristics of the causative factors, such as adverse environments (e.g., air travel, sitting near an air conditioner vent, low humidity), prolonged visual efforts (e.g., reading, computer use), or ameliorating circumstances (symptomatic relief with the use of artificial tears) is helpful in diagnosing dry eye. Supporting clinical observations and tests are used to confirm the diagnosis. A diagnostic classification scheme adapted from the 2007 Report of the International Dry Eye Workshop is shown in Figure 2.

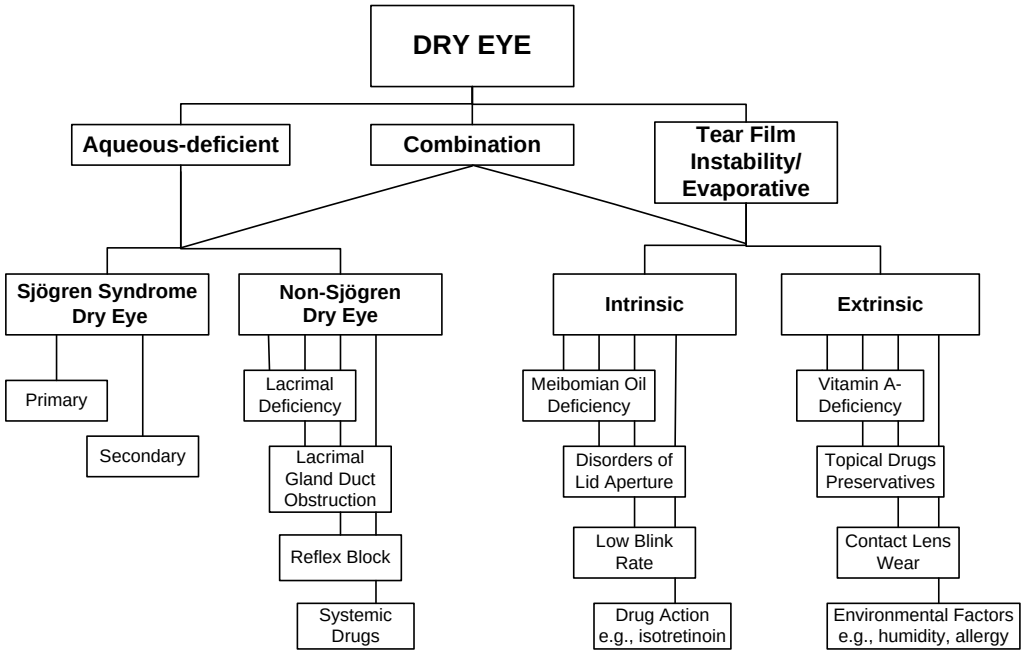

FIGURE 2. MAJOR ETIOLOGICAL CAUSES OF DRY EYE

Modified with permission from Lemp MA (Chair). Definition and Classification Subcommittee of the International Dry Eye Workshop. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). Ocul Surf 2007;5:77.

Participants in the workshop agreed that the two major factors, deficient aqueous tear production and increased evaporative loss, may cause dry eyes independently. They may also be present together and both contribute to dry eye symptoms and signs. Recent evidence suggests that evaporative dry eye is more common than a combined-mechanism dry eye. Aqueous tear deficiency alone is the least common presentation of dry eye, and this should be mentioned.[10] Most patients have multiple factors contributing to dry eye. Many conditions, such as neurotrophic keratitis after HSV infection or LASIK, include aspects of decreased tear production and increased evaporative loss.

History

Questions about the following elements of the patient history may elicit helpful information. There are several questionnaires that may be useful in completing the patient history, including the Ocular Surface Disease Index, the Dry Eye Questionnaire, and the Impact of Dry Eye on Everyday Life questionnaire.

- Symptoms and signs (e.g., irritation, tearing, burning, stinging, dry or foreign body sensation, mild itching, photophobia, blurry vision, contact lens intolerance, redness, mucous discharge, increased frequency of blinking, eye fatigue, diurnal fluctuation, symptoms that worsen later in the day)
- Exacerbating conditions (e.g., wind, air travel, decreased humidity, prolonged visual efforts associated with decreased blink rate such as reading and computer use)
- Duration of symptoms

The ocular history may include details about the following:

- Topical medications used, their frequency, and their effect on symptoms (e.g., artificial tears, eyewash, antihistamines, glaucoma medications, vasoconstrictors, corticosteroids, homeopathic or herbal preparations)
- Contact lens wear, schedule, and care
- Allergic conjunctivitis
- Ocular surgical history (e.g., prior keratoplasty, cataract surgery, keratorefractive surgery)
- Ocular surface disease (e.g., HSV, varicella zoster virus, ocular mucous membrane pemphigoid, Stevens-Johnson syndrome, aniridia, GVHD)
- Punctal surgery
- Eyelid surgery (e.g., prior ptosis repair, blepharoplasty, entropion/ectropion repair)
- Bell palsy

The medical history may take into account the following elements:

- Smoking or exposure to second-hand smoke
- Dermatological diseases (e.g., rosacea, psoriasis)
- Technique and frequency of facial washing, including eyelid and eyelash hygiene
- Atopy
- Menopause
- Systemic inflammatory diseases (e.g., Sjögren syndrome, GVHD, rheumatoid arthritis, systemic lupus erythematosus, scleroderma)
- Other systemic conditions (e.g., lymphoma, sarcoidosis)
- Systemic medications (e.g., antihistamines, diuretics, hormones and hormonal antagonists, antidepressants, cardiac antiarrhythmic drugs, isotretinoin, diphenoxylate/atropine, beta-adrenergic antagonists, chemotherapy agents, any other drug with anticholinergic effects)
- Trauma (e.g., mechanical, chemical, thermal)
- Chronic viral infections (e.g., hepatitis C, HIV)
- Nonocular surgery (e.g., bone-marrow transplant, head and neck surgery, trigeminal neuralgia surgery)
- Radiation of orbit
- Neurological conditions (e.g., Parkinson’s disease, Bell’s palsy, Riley-Day syndrome, trigeminal neuralgia)
- Dry mouth, dental cavities, oral ulcers
- Fatigue
- Joint pains/muscle aches

Examination

All patients should have a comprehensive adult medical eye evaluation at the recommended intervals.[69] The initial evaluation of a patient who presents with symptoms suggestive of dry eye should include those features of the comprehensive adult medical eye evaluation relevant to dry eye.[69]

The purpose of the external examination and the slit-lamp biomicroscopy is to do the following:

- Document the signs of dry eye
- Assess the quality, quantity, and stability of the tear film
- Determine other causes of ocular irritation

The external examination should pay particular attention to the following:

- Skin (e.g., scleroderma, facial changes consistent with rosacea, seborrhea)
- Eyelids: incomplete closure/malposition, incomplete or infrequent blink, eyelid lag or retraction, erythema of eyelid margins, abnormal deposits or secretions, entropion, ectropion
- Adnexa: enlargement of the lacrimal glands
- Proptosis
- Cranial nerve function (e.g., cranial nerve V [trigeminal], cranial nerve VII [facial])
- Hands: joint deformities characteristic of rheumatoid arthritis, Raynaud phenomenon, splinter hemorrhages underneath the nails

The slit-lamp biomicroscopy evaluation should focus on the following:

- Tear film: height of the meniscus, debris, increased viscosity, mucous strands, and foam, break-up time and pattern
- Eyelashes: trichiasis, distichiasis, madarosis, deposits
- Anterior and posterior eyelid margins: abnormalities of meibomian glands (e.g., orifice metaplasia, reduced expressible meibum, atrophy), character of meibomian gland secretions (e.g., turbid, thickened, foamy, deficient), vascularization crossing the mucocutaneous junction, keratinization, scarring
- Puncta: patency and position, presence and position of plugs
- Conjunctiva:
  - Inferior fornix and tarsal conjunctiva (e.g., mucous threads, scarring, erythema, papillary reaction, follicle enlargement, keratinization, foreshortening, symblepharon)
  - Bulbar conjunctiva (all four quadrants) (e.g., punctate staining with rose bengal, lissamine green, or fluorescein dyes; hyperemia; localized drying; keratinization, chemosis, chalasis, follicles)
- Cornea: localized interpalpebral drying, punctate epithelial erosions assessed with rose bengal, fluorescein or lissamine green dyes, punctate staining with rose bengal or fluorescein dyes, filaments, epithelial defects, basement membrane irregularities, mucous plaques, keratinization, pannus formation, thinning, infiltrates, ulceration, scarring, neovascularization, evidence of corneal or refractive surgery

Diagnostic Tests

A detailed review of systems should be performed for any patient who has clinically significant dry eye. Diagnostic testing is based on the review of systems and other clinical findings. High degree of suspicion is appropriate in patients who have clinically significant dry eye and dry mouth symptoms. In patients who are suspected of having a Sjögren syndrome, a serological examination for anti-Sjögren syndrome A antibody (SSA or anti-Ro), anti-Sjögren syndrome B antibody (SSB or anti-La), rheumatoid factor, and antinuclear antibody should be ordered. Patients who might have thyroid eye disease should be tested for antithyroid peroxidase antibody and antithyroglobulin antibody. A B-scan sonogram or other imaging study should be ordered to assess extraocular muscle thickness in patients who have suspected thyroid eye disease. Conjunctival biopsy is appropriate for any patients with significant chronic conjunctivitis with a nodular appearance or cicatrization (nodular conjunctivitis or subepithelial fibrosis). See Table 2 for a summary of diagnostic tests ordered for possible underlying systemic conditions in patients with dry eye.

Tear osmolarity has been thought to be an indicator of dry eye disease,[70] and a commercial device has recently become available for clinicians' use. Several studies using this device have demonstrated an increase in tear osmolarity in patients with aqueous tear deficiency or evaporative dry eye,[71,72] and it has been approved by the FDA for use as a point-of-care laboratory test to diagnose dry eye. However, several studies have failed to correlate tear osmolarity levels with clinical signs or patient symptoms,[73,74] and it is not clear that the test has great utility in the diagnosis of dry eye syndromes. See Appendix 4 for additional information about diagnostic tests.

TABLE 2 DIAGNOSTIC TESTS ORDERED FOR POSSIBLE UNDERLYING SYSTEMIC CONDITIONS IN PATIENTS WITH DRY EYE

Suspected Underlying Condition	Diagnostic Testing
Sjögren syndrome	SSA, SSB, ANA, RF
Thyroid eye disease	Anti-thyroid peroxidase antibody, antithyroglobulin antibody, B-scan sonogram to assess extraocular muscle thickness
Sarcoidosis	Serum lysozyme, ACE, chest CT to determine extent of disease (consult with a pulmonologist as necessary), conjunctival biopsy[75]
Cicatricial pemphigoid	Conjunctival biopsy with light microscopic as well as immunofluorescent or immunohistochemical studies

ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; RF = rheumatoid factor; SSA = anti-Sjögren syndrome A antibody (anti-Ro); SSB = anti-Sjögren syndrome B antibody (anti-La)

For patients with mild irritation symptoms, a rapid tear break-up time may indicate an unstable tear film with normal aqueous tear production, and there may be minimal or no dye staining of the ocular surface.[76] (See Appendix 4 for detailed descriptions of these tests.)

For patients with moderate to severe aqueous tear deficiency, the diagnosis can be made by using one or more of the following tests: tear break-up time test, ocular surface dye staining (rose bengal, fluorescein, or lissamine green), and the Schirmer test. These tests should be performed in this sequence because the Schirmer test can disrupt tear film stability and cause false-positive ocular surface dye staining. Several minutes should be allowed between the dye testing and the Schirmer test. Table 3 lists characteristic findings for each diagnostic test for each condition. Corneal sensation should be assessed when trigeminal nerve dysfunction is suspected.[77] A laboratory and clinical evaluation for autoimmune disorders should be considered for patients with significant dry eye, other signs and symptoms of an autoimmune disorder (e.g., dry mouth), or a family history of an autoimmune disorder.

Table 3 summarizes the clinical tests available for diagnosis of dry eye. No single test is adequate for establishing the diagnosis of dry eye. The constellation of findings from multiple tests adds greatly to the clinicians' understanding of dry eye. Conjunctival staining is a helpful sign, although its importance is underappreciated.

TABLE 3 CHARACTERISTIC FINDINGS FOR DRY EYE SYNDROME DIAGNOSTIC TESTING

	Test	Characteristic Findings
Aqueous tear deficiency	Ocular surface dye staining	Pattern of exposure zone (interpalpebral) corneal and bulbar conjunctival staining typical
	Tear break-up time	Less than 10 seconds considered abnormal
	Aqueous tear production (Schirmer test)	10 mm or less for Schirmer test with anesthesia considered abnormal[78,79]
	Fluorescein clearance test/tear function index	Test result is compared with a standard color scale[80]
	Lacrimal gland function	Decreased tear lactoferrin concentrations
	Tear osmolarity	Possibly increased with unclear clinical implications [71-74]
Evaporative tear deficiency	Ocular surface dye staining	Staining of inferior cornea and bulbar conjunctiva typical
	Tear break-up time	Less than 10 seconds considered abnormal
	Tear osmolarity	Possibly increased with unclear clinical implications[71-74]

CLASSIFICATION OF DRY EYE SYNDROME

Dry eye is generally classified according to a combination of symptoms and signs (see Appendix 5). In this PPP, dry eye has been classified as mild, moderate, and severe based on both symptoms and signs, but with an emphasis on symptoms over signs.[81] Due to the nature of dry eye disease, this classification is imprecise because characteristics at each level overlap.

Patients with mild dry eye syndrome may have symptoms of irritation, itching, soreness, ocular discomfort, burning, or intermittent blurred vision. The diagnosis of dry eye in its mild form is difficult to make because of the inconsistent correlation between reported symptoms and clinical signs[82] as well as the relatively poor specificity and/or sensitivity of clinical tests.[83,84] Patients can identify ocular dysesthesia related to contact lens wear or other cause as dryness, even when tear function is normal.[85,86] More effective relief of patient symptoms can be achieved if the ophthalmologist can differentiate conditions related to dry eye from other causes. Because most dry eye conditions have a chronic course, repeated observation and reporting of symptoms over time will allow clinical diagnosis of dry eye in most cases.

Patients with moderate dry eye syndrome have increased discomfort and frequency of symptoms, and the negative effect on visual function may become more consistent.

Patients with severe dry eye syndrome have an increasing frequency of symptoms that may become constant as well as potentially disabling visual symptoms.

Dry eye syndrome is also categorized into one of two forms, aqueous tear deficiency and evaporative tear deficiency. These conditions coexist in the majority of the patients with the disease.

MANAGEMENT

Patients with dry eye symptoms often have many contributory factors. It is imperative to treat any causative factors that are amenable to treatment. Tear replacement is frequently unsuccessful when used as the sole treatment if additional causative factors are not concomitantly addressed.

The ophthalmologist should educate the patient about the natural history and chronic nature of dry eye. Realistic expectations for therapeutic goals should be set and discussed with the patient. Patient education is an important aspect of successful management of this condition.

Table 4 lists treatments of dry eye syndrome according to the type of therapy used. Of these treatments, those particularly effective for evaporative tear deficiency include environmental modifications, eyelid therapy for conditions such as blepharitis or meibomianitis, artificial tear substitutes, moisture chamber spectacles, and/or surgery such as tarsorrhaphy.

Specific treatment recommendations depend on severity and cause. The sequence and combination of therapies should be determined on the basis of the patient's needs and preferences and the treating ophthalmologist's medical judgment. Table 5 lists treatments for dry eye syndrome based on the severity level of the disease. Specific therapies may be chosen from any category regardless of the level of disease severity, depending on physician experience and patient preference.

TABLE 4 CATEGORIES OF DRY EYE TREATMENTS

Type of Therapy	Treatment
Environmental/Exogenous	• Education and environmental modifications* (e.g., humidifier) • Elimination of offending topical or systemic medications
Medication	
Topical medication	• Artificial tear substitutes, gels/ointments* • Anti-inflammatory agents (topical cyclosporine and corticosteroids) • Mucolytic agents • Autologous serum tears
Systemic medication	• Omega-3 fatty acids (may increase prostate cancer risk in males) • Tetracyclines* (for meibomian gland dysfunction, rosacea) • Systemic anti-inflammatory agents • Secretagogues
Surgical	• Punctal plugs • Permanent punctal occlusion • Tarsorrhaphy* • Repair of eyelid malpositions or exposure* • Mucous membrane, salivary gland, amniotic membrane transplantation
Other	• Eyelid therapy (warm compresses and eyelid hygiene)* • Contact lenses • Moisture chamber spectacles*

Data from Pflugfelder SC (Chair). Management and Therapy Subcommittee of the International Dry Eye Workshop. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye Workshop (2007). Ocul Surf 2007;5:163-78.

* Particularly helpful for increased evaporative loss.

TABLE 5 TREATMENT RECOMMENDATIONS FOR DRY EYE SYNDROME BY DISEASE SEVERITY LEVEL

Mild	• Education and environmental modifications • Elimination of offending topical or systemic medications • Aqueous enhancement using artificial tear substitutes, gels/ointments • Eyelid therapy (warm compresses and eyelid scrubs) • Treatment of contributing ocular factors such as blepharitis or meibomianitis (see Blepharitis PPP[87]) • Correction of eyelid abnormalities
Moderate	*In addition to above treatments:* • Anti-inflammatory agents (topical cyclosporine[88,89] and corticosteroids[90-93]), systemic omega-3 fatty acids supplements[94,95] • Punctal plugs • Spectacle side shields and moisture chambers
Severe	*In addition to above treatments:* • Systemic cholinergic agonists[96-98] • Systemic anti-inflammatory agents • Mucolytic agents • Autologous serum tears[99,100] • Contact lenses • Permanent punctal occlusion • Tarsorrhaphy

Adapted with permission from Pflugfelder SC (Chair). Management and Therapy Subcommittee of the International Dry Eye Workshop. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye Workshop (2007). Ocul Surf 2007;5:174.

Mild Dry Eye

Because of the inconsistent correlation between reported symptoms and clinical signs[82] as well as the relatively poor specificity and/or sensitivity of clinical tests,[83,84] patients with suggestive symptoms without signs should be placed on trial treatments with artificial tears when other potential causes of ocular irritation have been eliminated. For patients with a clinical diagnosis of mild dry eye, potentially exacerbating exogenous factors such as antihistamine or diuretic use, cigarette smoking and exposure to second-hand smoke, and environmental factors such as air drafts (e.g., use of ceiling fans), and low-humidity environments should be addressed. Cigarette smoking has been found to be associated with dry eye because of the adverse effects on the lipid layer of the precorneal tear film and tear proteins.[101,102] Humidifying ambient air and avoiding air drafts by using shields and by changing the characteristics of airflow at work, at home, and in the car may be helpful. Measures such as lowering the computer screen to below eye level to decrease lid aperture,[103] scheduling regular breaks, and increasing blink frequency may decrease the discomfort associated with computer and reading activities.

As the severity of the dry eye increases, aqueous enhancement of the eye using topical agents is appropriate. Emulsions, gels, and ointments can be used. The use of artificial tears may be increased, but the practicality of frequent tear instillation depends on the lifestyle or manual dexterity of the patient. Nonpreserved tear substitutes are generally preferable; however, tears with preservatives may be sufficient for patients with mild dry eye and an otherwise healthy ocular surface. When tear substitutes are used frequently and chronically, (e.g., more than four times a day), nonpreserved tears are generally recommended.

Contributing ocular factors such as blepharitis or meibomianitis should also be treated (see Blepharitis PPP[87]). Topical azithromycin once daily has been shown to be effective in improving the contact lens wear time in patients with contact-lens-related mild dry eye in an open-label pilot study.[104] In light of a recent FDA warning regarding the risks of oral azithromycin use in patients who have cardiovascular problems,[105] this agent should be used with caution to treat dry eye in such individuals. Eyelid abnormalities resulting from blepharitis,[87] trichiasis, or lid malposition (e.g., lagophthalmos, entropion/ectropion) should be corrected.

Moderate Dry Eye

In addition to the treatments for mild dry eye, the following medications, surgical procedures, and other treatments may be helpful for moderate dry eye.

Anti-inflammatory therapies may be considered in addition to aqueous enhancement therapies. Cyclosporine is a fungus-derived peptide that prevents activation and nuclear translocation of cytoplasmic transcription factors that are required for T-cell activation and inflammatory cytokine production. It also inhibits mitochondrial pathways of apoptosis. In clinical trials submitted for FDA approval, topical cyclosporine 0.05% demonstrated a statistically significant 10 mm increase in Schirmer test results compared with vehicle at 6 months for those patients whose tear production was presumed to be decreased because of ocular inflammation. This effect was noted in 15% of cyclosporine-treated patients compared with 5% of vehicle-treated patients. While the drop is typically well tolerated, ocular burning was reported in 17% of the patients.[89] A subsequent small study demonstrated the efficacy of cyclosporine 0.05% in the treatment of dry eye in patients who had undergone punctal occlusion.[106] A recent study evaluated the efficacy of topical cyclosporine 0.05% in patients with mild, moderate, and severe dry eyes. They demonstrated success in 74%, 72%, and 67% of patients, respectively. The study had a minimum follow-up time of 3 months, because the authors believe it typically takes 3 months for the medication to take effect.[107] The dose can be decreased to once a day in a portion of the patients after one full year of twice-daily therapy without a decrease in beneficial effects.[108] Topical cyclosporine seemed to prevent progression of dry eye signs and symptoms over a period of 12 months in an open-label, single-center, small-scale prospective study when used twice daily.[109] However, insofar as dry eye symptoms tend to wax and wane over long periods of time, the lack of long-term data on the effectiveness of cyclosporine and the costs of longer-term (e.g., annual, lifetime) treatment should be weighed. It is also unclear whether the effects observed in these trials are clinically significant, and many subgroups of dry eye patients (e.g., those with MGD or keratoconjunctivitis sicca) are unlikely to experience the same benefits.

Corticosteroids have been reported to decrease ocular irritation symptoms, decrease corneal fluorescein staining, and improve filamentary keratitis.[90-92] In one study, a 2-week pretreatment of patients with a topical nonpreserved corticosteroid before punctal occlusion was reported to reduce ocular irritation symptoms and corneal fluorescein staining.[93] Commercially available loteprednol etabonate 0.5% was used in a prospective randomized study, and over 2 weeks of use, there was a beneficial effect in patients' symptoms and conjunctival hyperemia findings, but not in ocular surface staining, Schirmer test, or use of artificial tears. Extending the treatment to 4 weeks did not show any further beneficial effects or increase in side effect profile.[90] Low-dose topical corticosteroid therapy can be used at infrequent intervals for short periods of time (i.e., several weeks) to suppress ocular surface inflammation. Patients prescribed corticosteroids for dry eye should be monitored for adverse effects such as increased intraocular pressure and cataract formation.

Use of systemic omega-3 fatty acid supplements for dry eye treatment has been reported[110,111] to be potentially beneficial, but there is no evidence of their efficacy. An important obstacle in conducting high-quality trials of these supplements is the lack of standardization in the various formulations, in a largely unregulated industry. A double-masked study of 71 patients with mild to moderate dry eye syndrome demonstrated a non-statistically significant improvement in the Schirmer test, tear break-up time test, and fluorescein and lissamine green staining with the oral administration of polyunsaturated fatty acids.[94] Another study suggested that higher dietary intake of omega-3 fatty acids is associated with a decreased risk of dry eye syndrome in women.[95] However, a large case-control study suggested a link between intake of omega-3 fatty acids and increased risk of prostate cancer.[112]

For patients with aqueous tear deficiency, punctal occlusion is considered when the medical means of aqueous enhancement are ineffective or impractical. A Cochrane Collaboration review found limited evidence, from seven randomized controlled trials, that silicone plugs may provide symptomatic relief in patients with severe dry eye.[113] Punctal occlusion can be accomplished with non-absorbable materials such as silicone or thermal labile polymer plugs that are lodged at the punctal orifice in patients who will need long-term occlusion. The effectiveness in increasing the lower tear meniscus was similar with upper or lower tear duct occlusion.[114] Silicone plugs placed in the punctum have been shown to improve dry eye signs and symptoms, though in some patients they may irritate the conjunctival surface because of their shape.[113,115-117] Silicone plugs have the advantage of being removable if the patient develops symptoms of epiphora or irritation. These may be retained for many years without complications, provided they are appropriately sized. The largest plug that can be inserted should be used to reduce the likelihood of extrusion. One study found that 56% of silicone plugs were retained after 2 years, but in those patients whose plugs were spontaneously lost, 34% were reported to have canalicular stenosis at 2 years.[118] Patients who benefit from having punctal plugs in place but spontaneously lose them may have the lost plug(s) replaced or undergo permanent closure of their punctum by a thermal cautery or alternative means. Punctal plugs that are displaced into the lacrimal system may pass through the entire system, but blockage with secondary infection has been reported.[119,120] Rarely, surgical removal is necessary. Thermal labile polymer plugs are placed intracanalicularly. These have the advantage of not irritating the ocular surface. However, they have been associated with the occurrence of epiphora, canaliculitis, and dacryocystitis.[119]

Eyeglass side shields and moisture chambers are noninvasive therapies that can be used. These types of eyeglasses are frequently worn by motorcyclists and mountain climbers and can be purchased at stores or online. Moisture inserts (hydroxypropyl cellulose, Lacrisert, Aton Pharma, Inc., Lawrenceville, NJ) are occasionally helpful for patients who are unable to use frequent artificial tears.[121,122]

Severe Dry Eye

In addition to the treatments for mild and moderate dry eye, the following treatments may be considered for severe dry eye.

Oral medications are also available to treat severe dry eyes, especially for patients with combined dry eye and dry mouth (Sjögren syndrome).[96,97,123] Cholinergic agonists, pilocarpine, and cevimeline, have been approved by the FDA to treat the symptoms of dry mouth in patients with Sjögren syndrome. These medications bind to muscarinic receptors, which stimulate secretion of the salivary and sweat glands, and they appear to improve tear production. Most clinical studies demonstrate greater improvement in dry mouth than dry eye.[96,98] Patients treated with pilocarpine at a dose of 5 mg orally four times a day experienced a significantly greater overall improvement in the ability to focus their eyes during reading and in symptoms of blurred vision compared with placebo-treated patients.[96] The most common side effect from this medication was excessive sweating, which occurred in over 40% of patients. Two percent of the patients taking oral pilocarpine withdrew from the study because of this and other drug-related side effects. Cevimeline is another oral cholinergic agonist that has been found to improve ocular irritation symptoms and aqueous tear production.[97] This agent may have fewer adverse systemic side effects than oral pilocarpine.

Autologous serum drops have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients with Sjögren syndrome[99] and GVHD.[100]

Filamentary keratitis can be treated with debridement of the filaments or application of topical mucolytic agents, such as acetylcysteine 10% four times a day. Filaments can be debrided with a cotton-tip applicator, dry cellulose sponge, or jewelers' forceps. Soft contact lenses are effective in preventing recurrence of filamentary keratitis but are poorly tolerated if the patient has severe dry eye. If the patient has associated neurotrophic keratopathy, contact lenses should be avoided.

Permanent punctal occlusion can be accomplished by means of thermal or laser cautery. In general, laser cautery is not as effective as thermal cautery in achieving permanent, complete occlusion, and it is more expensive. The main disadvantage of punctal cautery is that it is not readily reversible. If occlusion with cautery is planned, a trial occlusion with nonpermanent implants generally should be performed first to screen for the potential development of epiphora. Silicone punctal plugs are more useful for this purpose. A stepwise approach to cautery occlusion is generally recommended so that no more than one punctum is cauterized in each eye at a treatment session. A limited tarsorrhaphy can be performed to decrease tear evaporation in patients with severe dry eye who have not responded to other therapies.[124]

Rigid gas-permeable scleral lenses have been employed successfully in the treatment of severe dry eye for years.[125-127] Widespread use of scleral lenses[128] may be limited by fitting difficulties (particularly in the presence of conjunctival cicatrization), patient willingness and ability to wear the lenses, and high costs. Soft contact lenses may have some usefulness and tolerance in selected cases, but they may provide symptomatic relief, particularly in the setting of filamentary keratitis. The use of contact lenses must be tempered by the risk of corneal infection.

Follow-up Evaluation

The purpose of the follow-up evaluation is to assess the response to therapy as a basis for altering or adjusting treatment as necessary, to monitor for structural ocular damage, and to provide reassurance. The frequency and extent of the follow-up evaluation will depend on the severity of disease, the therapeutic approach, and the response to the therapy. For example, patients with sterile corneal ulceration associated with dry eye may require daily follow-up.

PROVIDER AND SETTING

Because dry eye can be associated with systemic immunological disorders and the use of systemic medications, broad medical skills and training are important for appropriate diagnosis and management. Patients with dry eye who are evaluated by non-ophthalmologist health care providers should be referred promptly to the ophthalmologist if any of the following occurs:

- Moderate or severe pain
- Lack of response to the therapy
- Corneal infiltration or ulceration
- Vision loss

COUNSELING AND REFERRAL

The most important aspects of caring for patients with dry eye are to educate them about the chronic nature of the disease process and to provide specific instructions for therapeutic regimens. It is helpful to periodically reassess the patient's compliance and understanding of the disease, the risks for associated structural changes, and to re-inform the patient as necessary. The patient and physician together can establish realistic expectations for effective management.

Patients with severe dry eye are at greater risk for contact lens intolerance and associated complications. Patients with pre-existing dry eye should be cautioned that keratorefractive surgery, particularly LASIK, may worsen their dry eye condition.[129] Patients who have dry eye and are considering keratorefractive surgery should have the dry eye treated before surgery.[130] Uncontrolled dry eye syndrome is a contraindication for keratorefractive surgery.[131]

Referral of a patient with dry eye may be necessary, depending on the severity of the condition and its responsiveness to treatment. In moderate to severe cases that are unresponsive to treatment or when systemic disease is suspected, timely referral to an ophthalmologist who is knowledgeable and experienced in the management of these entities is recommended. Referral to an internist or rheumatologist can be considered for patients with systemic immune dysfunction or for those who require immunosuppressive therapy. Patients with systemic disease such as primary Sjögren syndrome, secondary Sjögren (associated with a connective-tissue disease), or connective tissue disease such as rheumatoid arthritis should be managed by an appropriate medical specialist. Patient support groups such as the Sjögren's Syndrome Foundation (www.sjogrens.org) may help patients adjust to their condition. Some patients may benefit from professional counseling as an aid in coping with the chronic disease state.

SOCIOECONOMIC CONSIDERATIONS

Dry eye is a common ocular condition with a prevalence as high as 33% in Japan.[132] In the United States, two large cross-sectional surveys, the Women's Health Study and the Physician's Health Studies, demonstrated that the prevalence of physician-diagnosed dry eye or severe dry eye symptoms was 7.8% in women and 4.3% in men 50 and older.[8,9] Claims data from a large U.S. managed care database (reflecting only individuals who seek medical care and are diagnosed with dry eye) suggest that the prevalence of clinically diagnosed dry eye is 0.4% to 0.5% overall and that it is highest among women and the elderly.[11]

A similar estimate was obtained from the Dry Eye Management Outcomes Simulation.[133] In this study, data from multiple sources were used to estimate medical costs and outcomes of dry eye. The prevalence in a typical managed care population was estimated at approximately 1%. Of these cases, about 60% are mild in severity, 30% moderate, and 10% severe. Of individuals with mild dry eye, only about 20% seek medical care compared with 50% of those with moderate disease and 100% of those with severe disease. This suggests that approximately 0.4% of individuals in a typical managed care population seek medical care for and are diagnosed with dry eye.

Dry eye has a considerable burden to the patient as well as the society. Studies suggest that dry eye is associated with significant impact on visual function such as reading and driving,[134] daily activities, social and physical functioning, workplace productivity, and quality of life.[26]

Although scarce, the existing data on the economics of dry eye suggest that the economic impact is substantial. Direct medical costs (e.g., office visits, prescription and over-the-counter medications, specialized eyewear, humidifiers, in-office procedures), direct nonmedical costs (e.g., patient

transportation), indirect costs (e.g., lost work time and productivity, changes in type of work), and intangible costs (e.g., reduced quality of life, lost leisure time, impaired social, emotional, and physical functioning) determine the total cost of dry eye to the patient as well as to society.[135,136] Three survey studies found that the impact of dry eye on health care utilization is substantial, particularly in patients with Sjögren syndrome.[137-139] Various studies reported that dry eye in patients with Sjögren syndrome in particular interfered with work an average of 184 to 200 days per year. It also caused 2 to 5 days of absenteeism per year,[137,139,140] with an estimated productivity loss of more than $5000 per patient per year.

In another study involving 2171 dry eye patients recruited from online databases, both the direct costs (i.e., ocular lubricants, cyclosporine, punctal plugs, physician visits, and nutritional supplements) and the indirect costs (i.e., productivity lost due to absenteeism) of their care were considered. The analysis estimated the average annual cost of treating a patient with dry eye at $783 (with a range of $757 to $809 across sensitivity analyses), and estimated the overall burden of such treatment to the U.S. health care system at $3.84 billion. From the societal perspective, the average cost of managing dry eye was estimated at $11,302 per patient and $55.4 billion for U.S. society overall.[141]

Dry eye is a chronic condition that is not curable. A number of therapies, mostly palliative, have been shown to improve symptoms of dry eye. Although it seems likely that these therapies would also improve quality of life and productivity and reduce overall health care utilization, few clinical studies have assessed patient-reported outcomes (e.g., quality of life), or economic measures, particularly the cost of therapy. Long-term topical treatment for dry eye syndrome is costly, and in the case of tear supplements, this cost is usually not covered by an insurance plan.

APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

Providing quality care
is the physician's foremost ethical obligation, and is
the basis of public trust in physicians.
AMA Board of Trustees, 1986

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients, and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.
  - The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn respond in an adequate and timely manner.

  - The ophthalmologist maintains complete and accurate medical records.
  - On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
  - The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
  - The ophthalmologist and those who assist in providing care identify themselves and their profession.
  - For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.
- Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices or procedures.
- The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

Reviewed by: Council
Approved by: Board of Trustees
October 12, 1988

2nd Printing: January 1991
3rd Printing: August 2001
4th Printing: July 2005

APPENDIX 2. PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades herein report the SIGN grade associated with the included studies supporting each recommendation (I++; I+; I-; II++; II+; II-; III), the GRADE evaluation of the body of evidence (Good, Moderate, Insufficient), and the GRADE assessment of the strength of the recommendation (Strong, Discretionary). Details of these grading systems are reported in the Methods and Key to Ratings section at the beginning of this document.

Highlighted Findings and Recommendations for Care

Page 4: Evaluation of conjunctival staining is helpful but underutilized: III; Insufficient; Discretionary

Page 4: Patients with moderate punctate staining of the cornea and/or conjunctiva should be considered for testing for an underlying Sjögren syndrome, as these patients will require a multidisciplinary approach: III; Insufficient; Discretionary

Page 4: Punctal plugs may be helpful in moderate to severe cases of aqueous deficient dry eye and meibomian gland dysfunction: I++; Good; Strong

Page 4: Patients treated with punctal plugs should be monitored regularly to ensure that the plugs are present and in the proper position: III; Insufficient; Discretionary

Page 4: Omega-3 fatty acid products without ethyl esters may be beneficial in the treatment of dry eye, though the evidence is insufficient to establish the effectiveness of any particular formulation: I-; Insufficient; Discretionary

Page 4: Cyclosporine treatment has been shown to have short-term clinical benefits in the treatment of dry eye: I+; Good; Strong

Care Process – Diagnosis

Page 9: Identifying characteristics of the causative factors, such as adverse environments, prolonged visual efforts, or ameliorating circumstances, is helpful in diagnosing dry eye: III; Good; Strong

Page 9: Supporting clinical observations and tests are used to confirm the diagnosis: III; Good; Strong

Page 10: Questions about patient symptoms and signs, exacerbating conditions, duration of symptoms, and ocular history may elicit helpful information: III; Good; Strong

Page 11: All patients should have a comprehensive adult medical eye evaluation at the recommended intervals: II++; Good; Strong

Page 11: The initial evaluation of a patient who presents with symptoms suggestive of dry eye should include those features of the comprehensive adult medical eye evaluation relevant to dry eye: II++; Good; Strong

Page 11: The external examination should pay particular attention to the skin, eyelids, adnexa, proptosis, cranial nerve function, and hands: III; Good; Strong

Page 11: The slit-lamp biomicroscopy evaluation should focus on the tear film, eyelashes, anterior and posterior eyelid margins, puncta, conjunctiva, and cornea: III; Good; Strong

Page 11: A detailed review of systems should be performed for any patient who has clinically significant dry eye: III; Good; Strong

Page 11: A high degree of suspicion is appropriate for patients who have clinically significant dry eye and dry mouth symptoms: III; Good; Strong

Page 11: Patients who might have thyroid eye disease should be tested for anti-thyroid peroxidase antibody and anti-thyroglobulin antibody: III; Insufficient; Discretionary

Page 11: A B-scan sonogram or other imaging study should be ordered to assess extraocular muscle thickness in patients who have suspected thyroid eye disease: III; Good; Strong

Page 11: Conjunctival biopsy is appropriate for any patients who have significant chronic conjunctivitis with a nodular appearance or cicatrization: III; Insufficient; Discretionary

Page 12: Several studies have failed to correlate tear osmolarity levels with clinical signs or patient symptoms, and it is not clear that the test has utility in the diagnosis of dry eye syndromes: II-; Moderate; Discretionary

Page 12: For patients with moderate to severe aqueous tear deficiency, the diagnosis can be made by using one or more of the following tests: tear break-up time test, ocular surface dye staining, and the Schirmer test: III; Insufficient; Discretionary

Page 12: These tests should be performed in this sequence because the Schirmer test can disrupt tear film stability and cause false-positive ocular surface dye staining: III; Insufficient; Discretionary

Page 12: Several minutes should be allowed between the dye testing and the Schirmer test: III; Insufficient; Discretionary

Page 12: Corneal sensation should be assessed when trigeminal nerve dysfunction is suspected: III; Moderate; Discretionary

Page 12: A laboratory and clinical evaluation for autoimmune disorders should be considered for patients with significant dry eye, other signs and symptoms of an autoimmune disorder, or a family history of an autoimmune disorder: III; Good; Strong

Page 13: Because most dry eye conditions have a chronic course, repeated observation and reporting of symptoms over time will allow clinical diagnosis of dry eye in most cases: III; Good; Strong

Care Process – Management

Page 13: The ophthalmologist should educate the patient about the natural history and chronic nature of dry eye: III; Good; Strong

Page 13: Realistic expectations for therapeutic goals should be set and discussed with the patient: III; Good; Strong

Page 13: Particularly effective treatments for evaporative tear deficiency include environmental modifications, eyelid therapy for conditions such as blepharitis or meibomianitis, artificial tear substitutes, moisture chamber spectacles, and/or surgery such as tarsorrhaphy: III; Insufficient; Discretionary

Page 13: The sequence and combination of therapies should be determined on the basis of the patient's needs and preferences and the treating ophthalmologist's medical judgment: III; Good; Strong

Page 13: Specific therapies may be chosen from any category regardless of the level of disease severity, depending on physician experience and patient preference: III; Good; Strong

Page 15: Patients who have suggestive symptoms without signs should be placed on trial treatments with artificial tears when other potential causes of ocular irritation have been eliminated: III; Insufficient; Discretionary

Page 15: For patients with a clinical diagnosis of mild dry eye, potentially exacerbating exogenous factors such as antihistamine or diuretic use, cigarette smoking and exposure to second-hand smoke, and environmental factors such as air drafts and low-humidity environments should be addressed: III; Good; Strong

Page 15: Measures such as lowering the computer screen to below eye level to decrease lid aperture, scheduling regular breaks, and increasing blink frequency may decrease the discomfort associated with computer and reading activities: III; Insufficient; Discretionary

Page 15: Emulsions, gels, and ointments can be used: III; Insufficient; Discretionary

Page 15: The use of artificial tears may be increased, but the practicality of frequent tear instillation depends on the lifestyle or manual dexterity of the patient: III; Insufficient; Discretionary

Page 15: Nonpreserved tear substitutes are generally preferable; however, tears with preservatives may be sufficient for patients with mild dry eye and an otherwise healthy ocular surface: III; Insufficient; Discretionary

Page 15: When tear substitutes are used frequently and chronically, nonpreserved tears are generally recommended: III; Insufficient; Discretionary

Page 15: Contributing ocular factors such as blepharitis or meibomianitis should also be treated: II++; Good; Discretionary

Page 15: Azithromycin should be used with caution to treat dry eye in patients who have cardiovascular problems: II+; Good; Strong

Page 15: Eyelid abnormalities resulting from blepharitis should be corrected: II++; Moderate; Discretionary

Page 15: Eyelid abnormalities resulting from trichiasis should be corrected: III; Insufficient; Discretionary

Page 15: Eyelid abnormalities resulting from lid malposition should be corrected: III; Insufficient; Discretionary

Page 16: Low-dose topical corticosteroid therapy can be used at infrequent intervals for short periods of time (i.e., several weeks) to suppress ocular inflammation: I-; Moderate; Discretionary

Page 16: Patients prescribed corticosteroids for dry eye should be monitored for adverse effects such as increased intraocular pressure and cataract formation: III; Good; Strong

Page 16: Use of systemic omega-3 fatty acid supplements for dry eye treatment has been reported to be potentially beneficial, but there is no evidence of their efficacy: I-; Insufficient; Discretionary

Page 16: For patients with aqueous tear deficiency, punctal occlusion is considered when the medical means of aqueous enhancement are ineffective or impractical: I++; Good; Strong

Page 16: The largest plug that can be inserted should be used to reduce the likelihood of extrusion: III; Insufficient; Discretionary

Page 16: Patients who benefit from having punctal plugs in place but spontaneously lose them may have the lost plug(s) replaced or undergo permanent closure of their punctum by a thermal cautery or alternative means: III; Insufficient; Discretionary

Page 16: Eyeglass side shields and moisture chambers are noninvasive therapies that can be used: III; Good; Strong

Page 16: Moisture inserts (hydroxypropyl cellulose, Lacrisert, Aton Pharma, Inc., Lawrenceville, NJ) are occasionally helpful for patients who are unable to use frequent artificial tears: III; Moderate; Discretionary

Page 17: Pilocarpine and cevimeline have been approved by the FDA to treat the symptoms of dry mouth in patients with Sjögren syndrome: I+; Moderate; Discretionary

Page 17: Autologous serum drops have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients with Sjögren syndrome: III; Insufficient; Discretionary

Page 17: Autologous serum drops have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients with GVHD: III; Insufficient; Discretionary

Page 17: Filamentary keratitis can be treated with debridement of the filaments or application of topical mucolytic agents, such as acetylcysteine 10% four times a day: III; Insufficient; Discretionary

Page 17: Filaments can be debrided with a cotton-tip applicator, dry cellulose sponge, or jewelers' forceps: III; Insufficient; Discretionary

Page 17: If the patient has associated neurotrophic keratopathy, contact lenses should be avoided: III; Good; Strong

Page 17: Permanent punctal occlusion can be accomplished by means of thermal or laser cautery: III; Good; Strong

Page 17: If occlusion with cautery is planned, a trial occlusion with nonpermanent implants generally should be performed first to screen for the potential development of epiphora: III; Insufficient; Discretionary

Page 17: A stepwise approach to cautery occlusion is generally recommended so that no more than one punctum is cauterized in each eye at a treatment session: III; Insufficient; Discretionary

Page 17: A limited tarsorrhaphy can be performed to decrease tear evaporation in patients with severe dry eye who have not responded to other therapies: III; Insufficient; Discretionary

Page 17: Rigid gas-permeable scleral lenses have been employed successfully in the treatment of severe dry eye for years: III; Insufficient; Discretionary

Provider and Setting

Page 18: Patients with dry eye who are evaluated by non-ophthalmologist health care providers should be referred promptly to the ophthalmologist if moderate or severe pain, lack of response to therapy, corneal infiltration or ulceration, or vision loss occurs: III; Good; Strong

Counseling and Referral

Page 18: The most important aspects of caring for patients with dry eye are to educate them about the chronic nature of the disease process and to provide specific instructions for therapeutic regimens: III; Good; Strong

Page 18: It is helpful to periodically reassess the patient's compliance and understanding of the disease, the risks for associated structural changes, and to re-inform the patient as necessary: III; Good; Strong

Page 18: Patients with pre-existing dry eye should be cautioned that keratorefractive surgery, particularly LASIK, may worsen their dry eye condition: III; Good; Strong

Page 18: Patients who have dry eye and are considering keratorefractive surgery should have the dry eye treated before surgery: III; Good; Strong

Page 18: In moderate to severe cases that are unresponsive to treatment or when systemic disease is suspected, timely referral to an ophthalmologist who is knowledgeable and experienced in the management of these entities is recommended: III; Good; Strong

Page 18: Referral to an internist or rheumatologist can be considered for patients with systemic immune dysfunction or for those who require immunosuppressive therapy: III; Good; Strong

Page 18: Patients with systemic disease such as primary Sjögren syndrome, secondary Sjögren, or connective tissue disease such as rheumatoid arthritis should be managed by an appropriate medical specialist: III; Good; Strong

Appendix 4: Diagnostic Tests

Page 29: Lissamine green dye is not recommended for evaluating corneal epithelial disease: III; Insufficient; Discretionary

Page 29: The Schirmer test can be performed to evaluate aqueous tear production, but it is well recognized that it gives variable results and should not be used as the sole criterion for diagnosing dry eye: III; Insufficient; Discretionary

APPENDIX 3. SJÖGREN SYNDROME

Sjögren syndrome is defined as dry eye and dry mouth associated with systemic immune dysfunction. About 10% of patients with clinically significant dry eye have an underlying Sjögren syndrome.[46,47] A significant proportion of the patients may not have been diagnosed at the time they present to the ophthalmology clinics with dry eye complaints.

Sjögren syndrome is characterized by infiltration of the lacrimal and salivary glands with lymphocytes with secondary compromise of gland function. Patients with primary Sjögren syndrome have unclassified systemic disease and symptoms that may include arthralgia, myalgia, or fatigue. Patients with primary Sjögren syndrome may also have associated thyroid dysfunction or autoimmune thyroiditis.[142] Patients with secondary Sjögren syndrome have a distinct autoimmune disease such as rheumatoid arthritis, scleroderma, or systemic lupus erythematosus. An epidemiologic study performed in Sweden reported that the prevalence of Sjögren syndrome is approximately 0.4%.[143] A Greek epidemiologic study reported the annual incidence of Sjögren syndrome as 5.3 per 100,000 and a prevalence of 92.8 cases per 100,000, with a female-to-male ratio of 20:1.[144] A study in Slovenia estimated the annual incidence of primary Sjögren syndrome as 3.9 per 100,000.[145] Women are much more commonly diagnosed with Sjögren syndrome than men.[146,147] Sjögren syndrome should be suspected if intrinsic tear-production deficiency is detected in nonelderly women, especially if it is rapid in onset and/or marked in severity. Diagnosis and treatment of underlying systemic immune disorders may decrease morbidity and may even be lifesaving. Patients with dry eye syndrome associated with Sjögren syndrome may develop other ocular manifestations of immune dysfunction, including scleritis, keratitis, and uveitis. Patients are also at increased risk for potentially life-threatening vasculitic lymphoproliferative disorders. Studies have shown that patients with decreased C4 levels at the time of diagnosis of Sjögren syndrome had a higher risk of developing lymphoma.[148,149]

Defined, objective criteria for diagnosing and classifying Sjögren syndrome have been proposed. According to comprehensive revised 2012 international criteria, diagnosis of Sjögren syndrome requires that at least two of the following three criteria be met:[150]

- Objective evidence of dry eyes (ocular surface staining score of 4 or more using lissamine green for bulbar conjunctiva and fluorescein for cornea based on a novel scoring system,[151] as shown in Figure A3-1)
- Positive serum anti-SSA and/or anti-SSB or positive rheumatoid factor or antinuclear antibody (titer >1:320)
- Presence of focal lymphocytic sialadenitis in labial salivary gland biopsy samples

Table A3-1 gives a summary of the evidence supporting different treatment options for dry eye associated with Sjögren syndrome.[152]

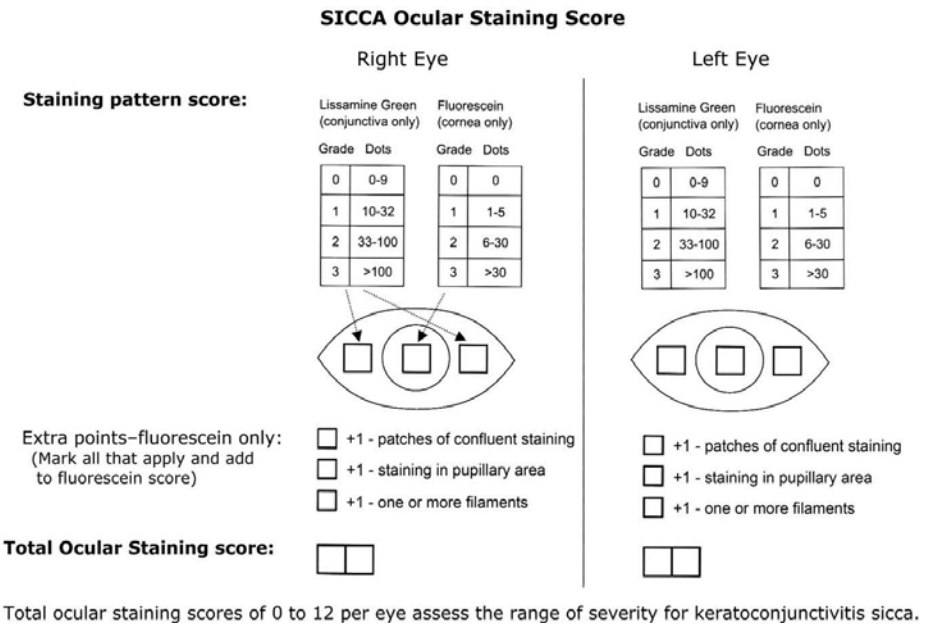

FIGURE A3-1. SJÖGREN'S INTERNATIONAL COLLABORATION CLINICAL ALLIANCE (SICCA) OCULAR STAINING SCORE FORM

Modified with permission from Whitcher JP, Shiboski CH, Shiboski SC, et al, for the Sjögren's International Collaborative Clinical Alliance Research Groups. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol 2010;149:407.

TABLE A3-1 SUMMARY OF EVIDENCE FOR THE TREATMENT OF DRY EYE ASSOCIATED WITH SJÖGREN SYNDROME

Treatment Modality	Strength of Evidence*	Clinical Recommendation†
Topical lubricants	II	A
Systemic secretagogues	II	B
Topical corticosteroids	III	B
Topical cyclosporine	II	A
Topical nonsteroidal anti-inflammatories	Insufficient	Not recommended
Punctal occlusion	II	B
Serum tears	II	B
Systemic dietary supplements	Insufficient	Not recommended
Systemic immunomodulatory treatments	Insufficient	Not recommended

Adapted with permission from Akpek EK, Lindsley KB, Adyanthaya RS, et al. Treatment of Sjögren's syndrome-associated dry eye. An evidence-based review. Ophthalmology 2011;118:1242-52.

* Strength of evidence is classified as follows:

- Level I indicates that the data provided strong evidence for the recommendation, the study design addressed the issue in question, and the study was performed in the population of interest and in a manner that ensured accurate and reliable data, using appropriate statistical methods.
- Level II indicates that the data provided substantial evidence for the recommendation but lacked some components of level I.
- Level III indicates a weaker body of evidence not meeting the criteria of levels I or II, such as expert opinions, small case series, and case reports.

† Clinical recommendations are classified as follows:

- A indicates that the recommendation is very important or crucial to a good clinical outcome.
- B indicates that the recommendation is moderately important to clinical outcome.
- C indicates that the recommendation is not definitively related to clinical outcome.

APPENDIX 4. DIAGNOSTIC TESTS

This appendix summarizes the applicability of currently utilized tests to diagnose tear film and ocular surface disorders. These tests include the tear break-up time test to evaluate tear-film stability, ocular surface dye staining to evaluate ocular surface disease, the Schirmer test and fluorescein clearance test to evaluate aqueous tear production and clearance, and the tear osmolarity test.

TEAR BREAK-UP TIME TEST

Tear break-up time is determined by instilling fluorescein dye in the inferior cul-de-sac and then evaluating the stability of the precorneal tear film.[76] The test is performed by moistening a fluorescein strip with sterile nonpreserved saline and applying it to the inferior tarsal conjunctiva. Fluorescein-anesthetic combination drops are not ideal for this purpose, as the anesthetic may affect the result of the test. After several blinks, the tear film is examined using a broad beam of the slit-lamp biomicroscope with a cobalt blue filter. The time lapse between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein-stained tear film is the tear break-up time. The tear break-up time should be evaluated before the instillation of any eye drops and before the eyelids are manipulated in any way.

Recurrent tear break-up in the same area may indicate localized anterior basement-membrane abnormalities. Break-up times less than 10 seconds are considered abnormal.[76] A rapid tear break-up time is observed in both aqueous tear deficiency and meibomian gland disease (MGD).[76]

OCULAR SURFACE DYE STAINING

Fluorescein, rose bengal, or lissamine green dyes may be used to assess the ocular surface.

Fluorescein dye stains areas of the corneal and conjunctival epithelium where there is sufficient disruption of intercellular junctions to allow the dye to permeate into the tissue.[153] Saline-moistened fluorescein strips or 1% to 2% sodium fluorescein solution is used to stain the tear film. After instilling the dye, the ocular surface is examined through a biomicroscope using a cobalt blue filter. Staining may become more apparent after 1 to 2 minutes, and it is more intense when it is observed with a yellow filter. Mild fluorescein staining can be observed in normal eyes and may be more prominent in the morning. Exposure-zone punctate or blotchy fluorescein staining is observed in dry eye, and staining is more easily visualized on the cornea than on the conjunctiva.

Rose bengal staining of the tear film may be performed using a saline-moistened strip or 1% solution. (Patients should be informed that the drop might irritate the eye.) The saline drop used to moisten the strip should remain in contact with the strip for at least a minute to achieve an adequate concentration of rose bengal to stain the ocular surface. Rose bengal staining is more intense on the conjunctiva than on the cornea. The dye stains ocular surface cells that lack a mucous coating as well as debris in the tear film[153]; the staining may be easier to observe with a red-free filter.

Lissamine green dye has a staining profile similar to that of rose bengal,[154-156] but it causes less ocular irritation.[155,156] It is not recommended for evaluating corneal epithelial disease.

Diffuse corneal and conjunctival staining is commonly seen in viral keratoconjunctivitis and medicamentosa. Staining of the inferior cornea and bulbar conjunctiva is typically observed in patients with staphylococcal blepharitis, MGD, lagophthalmos, and exposure, whereas staining of the superior bulbar conjunctiva is typically seen in superior limbic keratoconjunctivitis. A pattern of exposure zone (interpalpebral) corneal and bulbar conjunctival staining is typically seen with aqueous tear deficiency.[157,158]

SCHIRMER TEST

The Schirmer test can be performed to evaluate aqueous tear production, but it is well recognized that it gives variable results and should not be used as the sole criterion for diagnosing dry eye. It is performed by placing a narrow filter-paper strip in the inferior cul-de-sac. Aqueous tear production is measured by the length in millimeters that the strip wets during the test period, generally 5 minutes.[158] Schirmer testing may be performed with or without the use of topical anesthesia. The Schirmer test with anesthesia, also referred to as a basic secretion test, has been reported to give more variable

results than the Schirmer test done without anesthesia.[84] Results of 10 mm or less for the Schirmer test with anesthesia are generally considered abnormal.[78,79] If topical anesthesia is applied, excess fluid should be gently removed from the cul-de-sac prior to insertion of the filter paper. Although no absolute cutoff has been established for this test, less than 10 mm of strip wetting in 5 minutes is suggestive of abnormality in patients tested without anesthesia.[76] While an isolated abnormal result can be nonspecific, serially consistent low results are highly suggestive of aqueous tear deficiency.

FLUORESCEIN CLEARANCE TEST/TEAR FUNCTION INDEX

The clearance or turnover of tears on the ocular surface can be assessed using a number of tests, including the fluorescein clearance test and tear function index.[80,159] These tests are performed by instilling a measured amount of fluorescein dye on to the ocular surface, then assessing clearance of the dye by visually comparing the residual dye in the inferior tear meniscus of the Schirmer strip that has been placed onto the ocular surface with a standard color scale.[80,159] This test assesses aqueous tear production, tear volume, and tear drainage. It has been found to show better correlation with the severity of ocular irritation symptoms and corneal fluorescein staining than the Schirmer test.[160,161]

TEAR OSMOLARITY TEST

Tear osmolarity has long been thought to be a key feature of dry eye.[162-164] However, the test did not gain popularity until after the Food and Drug Administration (FDA) clearance of a commercially available device (TearLab, San Diego, CA) in 2009 to be used as a point-of-care laboratory test to diagnose dry eye. Since then a number of studies have been published reporting on the utility of this device. A current review of the literature demonstrates conflicting results. There are a number of studies published by independent researchers suggesting that osmolarity exhibits the strongest correlation with disease severity of any single objective metric in clinical use[71,165-168] and predicting response to therapeutic interventions.[169-171] However, tear osmolarity has also been criticized by others for its lack of correlation to symptoms and to the other objective dry eye signs.[74,172]

One inherent problem with using tear film osmolarity is that our understanding of this parameter is currently limited. For example, just very recently a tear osmolarity >305 mOsm/L was selected as the cut-off value for diagnosing dry eye. However, at a cutoff of 312 mOsms/L, tear hyperosmolarity is noted to have 73% sensitivity and 92% specificity for diagnosing dry eye.[71] By contrast, the other clinical tests commonly used in diagnosing dry eye have either poorer sensitivity (corneal staining, 54%; conjunctival staining, 60%; meibomian gland grading, 61%) or specificity (tear film break-up time, 45%; Schirmer test, 51%). However, these numbers, in isolation, are not particularly helpful and should be considered within the context of symptoms and other clinical findings. Understanding of osmolarity values in normal patients as well as in patients with dry eye is still evolving. Rather than relying solely on the absolute number measured with the device, correlation with clinical findings or differences in osmolarity over time or under different conditions would seem to be more important to confirm the diagnosis of dry eye. Indeed, most recent studies confirm that normal subjects have exceptionally stable tear film osmolarity, whereas dry eye subjects become unstable quickly and lose homeostasis with environmental changes.[70] These data reinforce the long-held belief that tear film "instability" is a core mechanism of the disease, and conveniently, tear osmolarity provides a good measure of this characteristic. The importance of tear osmolarity will become more clear over time.

Another issue that may become more clear over time is whether the use of osmolarity measurement is cost-effective. There is cost associated with the purchase of the machine and with its per patient use. This cost must be borne by the patient and/or the third-party payor. Tear osmolarity is perhaps not necessary for management of dry eye in an ophthalmology practice. In the hands of a rheumatologist or general practitioner, unable to do a comprehensive external or slit-lamp examination, it may be of benefit. More research and experience with this measurement device will help determine its value and clinical relevance.

APPENDIX 5. DRY EYE SEVERITY GRADING SCHEMES

Many classification systems for dry eye severity exist; Tables A5-1 and A5-2 represent two commonly used systems. Table A5-1 outlines a grading scheme devised by an expert group to classify dry eye severity.[173]

TABLE A5-1 DRY EYE SEVERITY GRADING SCHEME

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental 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

Reproduced with permission from Lemp MA (Chair). Definition and Classification Subcommittee of the International Dry Eye Workshop. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). Ocul Surf 2007;5:88.

TFBUT = fluorescein tear break-up time; MGD = meibomian gland disease

* Must have signs AND symptoms.

Table A5-2 outlines a classification system for dysfunctional tear syndrome (DTS).

TABLE A5-2 LEVELS OF SEVERITY OF DTS WITHOUT LID MARGIN DISEASE ACCORDING TO SYMPTOMS AND SIGNS

Severity*	Patient Profiles
Level 1	• Mild to moderate symptoms and no signs • Mild to moderate conjunctival signs
Level 2	• Moderate to severe symptoms • Tear film signs • Mild corneal punctate staining • Conjunctival staining • Visual signs
Level 3	• Severe symptoms • Marked corneal punctate staining • Central corneal staining • Filamentary keratitis
Level 4	• Severe symptoms • Severe corneal staining, erosions • Conjunctival scarring

Reproduced with permission from Behrens A, Doyle JJ, Stern L, et al, Dysfunctional Tear Syndrome Study Group. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 2006;25:904.

DTS = dysfunctional tear syndrome

* At least one sign and one symptom of each category should be present to qualify for the corresponding level assignment.

RELATED ACADEMY MATERIALS

Basic and Clinical Science Course

External Disease and Cornea (Section 8, 2013–2014)

Patient Education Brochures

Dry Eye (2012)
Dry Eye (Spanish – Ojo Seco) (2012)

Patient Education Communication Tools

Digital-Eyes™ Ophthalmic Animations for Patients Subscription (2009) (also available in Spanish)

Patient Education PowerPoint® Presentations

The Eye Over Time (2009)

Preferred Practice Pattern® Guidelines – Free download available at www.aao.org/ppp.

Comprehensive Adult Medical Eye Evaluation (2010)

To order any of these products, except for the free materials, please contact the Academy's Customer Service at 866.561.8558 (U.S. only) or 415.561.8540 or www.aao.org/store.

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