Improving Diagnosis and Outcomes of Sjögren's Disease through Targeting Dry Eye Patients: A Continuing Medical Education Enduring Material

I. INTRODUCTION

Sjögren's disease, or Sjögren's syndrome as the condition has until recently been known, is a common autoimmune disorder.[1] An inflammatory condition that affects many parts of the body but particularly the exocrine glands, Sjögren's disease causes dryness of mucosal surfaces, most frequently those of the eyes and mouth. In surveys conducted by the Sjögren's Syndrome Foundation (SSF), dry eye has consistently been named the feature of Sjögren's disease that disturbs patients' quality of life the most. Dry eye symptoms are typically what motivate Sjögren's disease patients to seek medical attention, with the result that eyecare practitioners are the ones who most often initially encounter Sjögren's disease.[2]

The dry eye of Sjögren's disease can produce significant ocular discomfort. Patients complain of sensations of grittiness, stinging, and burning, as well as visual disturbances, particularly when reading or performing intense near vision tasks. Historically, however, patients have faced long delays in diagnosis of the disease, with some studies suggesting that it can take as long as 7 years from onset of symptoms to diagnosis.[2] Although this delay is due in part to the subtle, confusing signs and symptoms of early Sjögren's disease, the lack of awareness in both the general and medical communities regarding the frequency and morbidity of the disease contributes to this delay. Early diagnosis of Sjögren's disease is critical so that patients can be effectively treated and monitored for serious complications including lymphoma.

Since eyecare providers are often the first medical professionals to encounter patients with Sjögren's disease, it is imperative that they be alert to the possibility of the disease in any patient who presents with a dry eye. Because Sjögren's disease affects multiple body systems, eyecare professionals should have close working relationships with other health care providers—including oral health professionals, endocrinologists, and especially rheumatologists—to assure comprehensive, collaborative care.

In the following pages, we review our current understanding of dry eye disease (DED), including its relationship to Sjögren's disease. We discuss the methods available to diagnose DED and some of the diagnostic challenges that eyecare practitioners face. Because Sjögren's disease represents a significant but often overlooked subset of DED patients, we offer a protocol for selecting those who should be identified for additional testing as potential Sjögren's disease patients. Finally, we offer an approach to management of Sjögren's disease patients and describe resources available to them.

Our goal throughout is to provide tools that will enable eyecare practitioners to more readily identify Sjögren's and other autoimmune disease patients in the DED population. Earlier initiation of appropriate treatment can reduce suffering, improve quality of life, and lead to better outcomes.

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II. A DED TAXONOMY

The past two decades have witnessed an explosion of research in DED, with growing awareness of it as a significant cause of ocular morbidity. Numerous expert consortia have attempted to gather and distill evidence-based data about DED into clinically useful classification schemes and recommendations for care. As always, guidelines are merely guidelines. However, due to the complex nature of DED etiology, the multiplicity of diagnostic tools and schema, and an ever-evolving knowledge base, research summaries and practice recommendations continue to provide an important basis for communication within this young field. Highlights from these and other sources are presented below.

A. Definition and Scope of DED

The 2007 International Dry Eye Workshop (DEWS) report defined DED as "*a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.*"[1] Consistent with the DEWS report, the American Academy of Ophthalmology (AAO) Preferred Practice Pattern Guidelines of 2013 separate DED into two main

OUTLINE

categories: DED due to "reduced tear production," and DED due to "excessive tear evaporation."[2]

Practice guidelines from the America Optometric Association (AOA) refer to "dry eye" as any condition that results from "aqueous deficiency or disruption" and acknowledge that different ocular surface disorders related to dry eye can "overlap as well as coexist."[3] Dry eye is considered treatable but generally not curable.[2]

Perhaps the best way to characterize DED is as a breakdown or disruption of some aspect of the lacrimal functional unit, which is comprised of the conjunctiva, cornea, lacrimal and meibomian glands, lacrimal drainage system, preocular tear film, and reflexive neural connections.[4] An intact lacrimal functional unit maintains homeostasis of the ocular surface via the production, distribution, and drainage of a clear, balanced tear film. Dysfunction of the lacrimal functional unit at any level can initiate a cascade of downstream events and provide an initial impetus for the development of DED.

B. Prevalence of DED

As there is no single test (nor universally accepted sequence of tests) for the diagnosis of DED, and as patient-reported symptoms are often poorly concordant with objective assessments, the exact prevalence of DED is difficult to ascertain. However, using the most restrictive definition of DED, nearly 5 million individuals in the US suffer from the condition, and many millions more presumably have subclinical or intermittent expressions of the disease.[5] Employing various diagnostic criteria and investigating diverse populations, different surveys have shown between 5% and 33% DED prevalence, with the greatest prevalence found among Asian, female, and older populations.[5] Among proposed risk factors for DED, those

Table II-1. Major Dry Eye Disease Categories, Primary vs. Secondary

Primary Dry Eye		Secondary Dry Eye	
Primary Evaporative	**Primary Aqueous Deficiency**	**Secondary to Systemic Disease**	**Secondary to Local Abnormality**
MGD	Non-Sjögren's disease	Sjögren's disease SLE RA MCTD	Lid dysfunction Trauma Blink Disorder

MGD = meibomian gland disease; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; MCTD = mixed connective tissue disease

most consistently supported by the literature include older age; female sex; exposure to postmenopausal estrogen replacement therapy, antihistamines, or radiation therapy; deficiency in androgens, vitamin A, or dietary omage-3 fatty acids; connective tissue disease; hepatitis C infection; LASIK or other refractive excimer laser surgery; and hematopoietic stem cell transplantation. Myriad other DED risk factors have been suggested, from smoking to antidepressants to botulinum toxin (Botox®); however, evidence for these is less certain at this time.[2]

Recently, lifestyle and environmental factors—including prolonged computer use (which decreases blink rate), low humidity environments, and contact lens wear—have also been implicated as risk factors for the development and progression of DED.[4]

C. DED Morbidity

Morbidity associated with DED is significant and frequently underestimated by practitioners. DED-related ocular symptoms can reduce quality of life, with effects on psychological, social, work-related, and physical functioning.[6,7] Difficulty with activities of everyday living, including driving, reading, working, and leisure activities, are approximately three times more common among patients with DED than among unaffected populations.[6] DED also contributes to contact lens intolerance and poor outcomes following ocular surgery.[5] In a revealing and oft-quoted disease utility study, patients with moderate DED had quality-of-life impairment scores that were very similar to the scores of patients with moderate angina.[8]

Patients with DED can experience a significant compromise in visual functioning. Common complaints and findings associated with moderate to severe DED include visual blurring that improves with a blink, reduced contrast sensitivity, and impaired visual acuity.

The incidence of DED increases with age; and without improvements in prevention, detection and therapy, morbidity and disease burden related to DED is expected to grow as the population ages.[5]

D. Clinical Presentation of DED

Patients with DED typically present with complaints of ocular surface burning, stinging, irritation, itching, soreness, general discomfort, and/or frank dryness.[2,3] Symptoms may

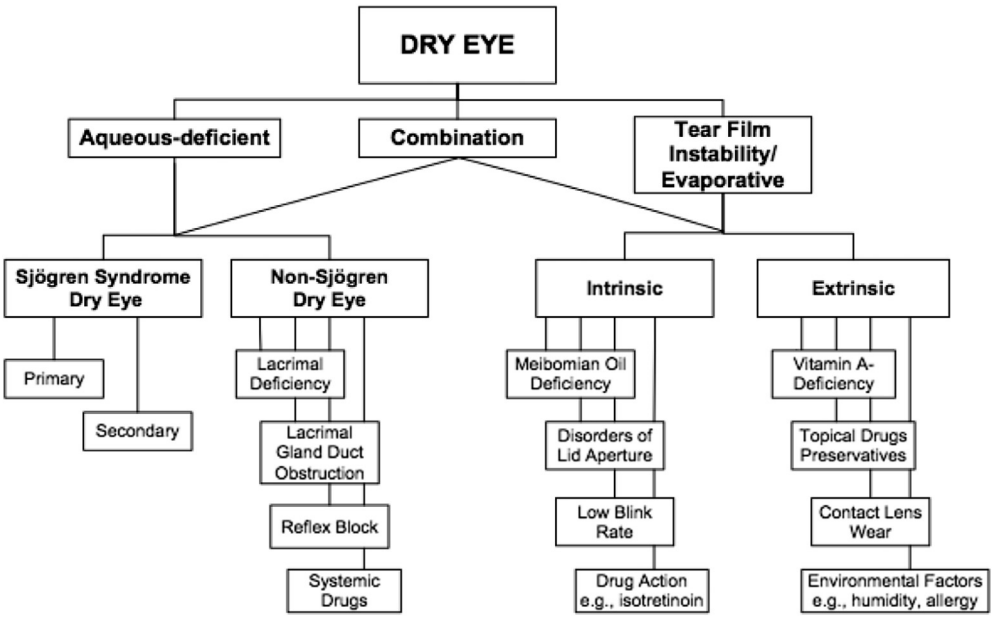

Figure II-1. Major Dry Eye Disease Categories, Aqueous Deficient vs. Evaporative Modified from Figure 2 in American Academy of Ophthalmology Cornea/External Disease Panel. *Preferred Practice Pattern® Guidelines. Dry Eye Syndrome.* San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp. The figure is adapted from the DEWS Report.

Table II-2. 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

* Must have signs AND symptoms.

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

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.

Modified from Table A5-1 in 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. The table is adapted from the DEWS Report.

be noticeable or worsened under circumstances of prolonged visual focus (eg, computer work or reading), especially in the later hours of the day. Symptoms may also worsen under the influence of certain medications (eg, antihistamine-containing cold or allergy remedies) or under adverse environmental conditions, such as air conditioning or a particularly dry climate. In these circumstances, patients may experience an increasing need for topical ocular lubricating agents (eg, artificial tears) for symptom relief.[2]

Early in the course of disease, an insufficient and/or unstable tear film may result in symptoms that are mild, intermittent, and/or brought about only by internal or external stressors. As tear film hyperosmolarity and inflammation increase, symptoms may become more severe and persistent and may include visual complaints.[3]

An often-cited feature of DED is that patient-reported symptoms frequently do not correlate with objective signs of disease.[9,10] In one study among patients with objective signs of DED, slightly more than half complained of symptoms.[10] While the basis for the disparity between subjective and objective findings in DED is not clear, corneal hypoesthesia related to prolonged inflammation and superficial corneal tissue disruption may be a contributing factor.[11]

E. Forms of DED

DED is generally classified by etiology. Patients whose DED does not stem from an identifiable extraocular source (such a systemic disorder or eyelid abnormality) are classified as having "primary" DED. Primary DED is typically divided into evaporative dry eye—most often caused by meibomian gland dysfunction (MGD)—or aqueous deficient dry eye. DED may be classified as "secondary" when an underlying etiologic mechanism can be identified; these mechanisms include systemic diseases (eg, Sjögren's disease, systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], or mixed connective tissue disease [MCTD]) and anatomic or neurologic ocular conditions (eg, blink disorder, lid abnormality, or trauma). (Table II-1.)

A separate means for categorizing DED put forth by the DEWS committee starts with divisions between aqueous deficient and evaporative mechanisms, then subdivides by primary or secondary causation.[1] (Figure II-1.)

F. Aqueous Deficient DED

Aqueous deficient DED, which results from impaired production of lacrimal fluid, is divided into Sjögren's disease and non-Sjögren's disease forms. Sjögren's disease is

Table II-3. Dry Eye Disease 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 cylosporine 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*

* Particularly helpful for increased evaporative loss.

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. Modified from Table 4 in 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. The table is adapted from the DEWS Report.

sometimes further divided into primary and secondary forms, ie, secondary to other autoimmune disease such as SLE, RA, MCTD, or other.

Some experts have questioned the use of a category for Sjögren's disease secondary to another autoimmune disease, proposing instead that patients with two autoimmune diseases be identified without primary and secondary designations.[12] They argue that until the etiology is understood, we cannot know which process came first and therefore should not make presumptions.

However, among Sjögren's disease patients, there is value in attempting to determine which autoimmune process is primary, as internal manifestations and prognosis may differ between the two. For example, unlike patients with primary Sjögren's disease, those with secondary Sjögren's disease have not been shown to be at increased risk of lymphoma. Thus, primary and secondary Sjögren's disease may well represent slightly different disease processes.[13] On occasion, two rheumatologic conditions occur simultaneously and/or are diagnosed at the same time. In such instances, a clear primary and secondary designation cannot be made and the designation of "overlap syndrome" is used. In instances where individuals have signs and symptoms of a connective disorder, including DED, but fail to meet any criteria for a specific autoimmune disease, the term "undifferentiated connective tissue disease" is used.

G. Evaporative DED

In contrast to aqueous deficient forms of DED, evaporative DED is the result of impaired production or balance of lipid and/or mucin components of the tear film or impaired eyelid/blink function. The most common cause of evaporative DED (and the most common form) is MGD.[14]

MGD results from hyperkeratinization of ductal epithelial cells and subsequent blockage of terminal meibomian gland ducts, or by accumulation of abnormally thick meibomian secretions. Gland obstruction leads to cystic dilation, meibocyte death, gland dropout, and reduced meibum secretion. Reduced meibum in the tear film and insufficient meibum quality causes evaporative dry eye, hyperosmolarity, tear film instability, and local bacterial overgrowth. Age, gender, endogenous and exogenous hormones, and topical medications may all play a role in MGD development.[14]

A prolonged interval between blinks (as may occur with blink abnormalities or computer use), as well as drying medications and environments, can also cause or exacerbate evaporative DED. In terms of prevalence, evaporative DED > mixed evaporative/aqueous deficient DED > aqueous deficient DED.[2,5]

H. Primary DED Treatment Options

DED can also be categorized according to severity without respect to etiopathogenesis, as many etiologic

Table II-4. Dry Eye Disease Treatment by Severity

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 cydosporine[88,89] and corticosteroids[90-93]), systemic omega-3 fatty acids supplements[94,96] • Punctal plugs • Spectade 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 ocdusion • 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.

Modified from Table 5 in 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. The table is adapted from the DEWS Report.

mechanisms and combinations of mechanisms result in similar downstream signs and symptoms. (Table II-2) Staged treatment algorithms for DED are often based on severity rather than etiology.

Our evolving understanding of DED pathophysiology has led to increasingly sophisticated management strategies in which the entire lacrimal functional unit is considered. The current management paradigm goes beyond ocular surface rehydration and lubrication to include improving glandular health and function, combating inflammation, and maintaining ocular surface epithelial barrier integrity. Optimally, treatment will address underlying and contributing factors as well as disease severity. Aggressive treatment early in the course of disease can improve quality of life and protect patients from serious, even sight-threatening, complications.[15]

DED treatment options may be categorized by type into: (1) environmental/exogenous; (2) topical medication; (3) systemic medication; (4) surgical; and (5) other. (Table II-3) Disease severity and patient response to prior treatments are major considerations when crafting a DED therapeutic regimen. (Table II-4) DED treatment is thoroughly covered in other reviews.[2,3,15] Clinical guidelines for management of dry eye disease developed by the Sjogren's Syndrome Foundation have been recently been published.[16] Details related to DED treatment among Sjögren's disease patients is presented in section VI: Sjögren's Disease Management.

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III. SJÖGREN'S DISEASE: THE DISEASE STATE

Sjögren's disease is a chronic autoimmune disease of the exocrine glands characterized principally by lymphocytic infiltration and damage to lacrimal and salivary glands, commonly resulting in aqueous deficient DED.[1] Its unique pathogenesis, array of clinical findings, and prognosis distinguish it from other forms of aqueous deficient DED. Furthermore, it is not unusual for Sjögren's disease patients to have evidence of MGD in addition to aqueous deficiency.[2] The vast majority of patients with Sjögren's disease present with insidious onset of sicca symptoms that evolve over a period of months to years. A minority of patients, perhaps 20%, present in an atypical fashion, with minimal or nil sicca symptoms. (Table III-1)

Studies suggest that quality of life for Sjögren's disease patients is poor and generally comparable to that of patients with other rheumatic diseases.[3,4] Fatigue and musculoskeletal pain are two of the most important contributors to poor quality of life among Sjögren's disease patients.[5] In England, annual healthcare costs for Sjögren's disease were found to be more than twice those of community controls (£949) and comparable (£2,188 vs. £2,693) to those of patients with RA.[6] In another study, dental care costs are significantly increased in Sjögren's disease patients compared to normal controls.[7]

Since 1965, 12 classification schemes for the diagnosis of Sjögren's disease have been proposed, the two most recent being the revised American-European Consensus Group (AECG) and the American College of Rheumatology (ACR) classification schemes.[8,9] The revised AECG classification criteria defines six components of the evaluation—ocular symptoms, oral symptoms, ocular signs, oral signs, labial minor salivary gland biopsy, and presence of marker autoantibodies. (Table III-2) A diagnosis of primary Sjögren's disease requires that four of six categories be positive, including either lip biopsy or the marker autoantibodies; diagnosis of secondary Sjögren's disease requires the presence of at least one ocular or oral complaint in a patient with established connective tissue (eg, RA) plus at least two of the following: positive ocular sign, oral sign or lip biopsy.[9] The AECG criteria can facilitate the diagnosis of Sjögren's disease even in patients who don't have a lip biopsy or in patients who do not have sicca symptoms. Nevertheless, sicca symptoms comprise an important part of this classification scheme.

Table III-1. Unusual Presentations of Sjögren's disease

Seropositive polyarthritis	Renal tubular acidosis
Polymyalgia rheumatica	Fever of unknown origin
Leukocytoclastic vasculitis	Chronic fatigue syndrome
Peripheral neuropathy	Elevated ESR
Demyelinating disease	Positive ANA or RF in an asymptomatic patient
Inflammatory myositis	Corneal melt or perforation
Salivary gland swelling	
Accelerated caries	

ANA = antinuclear antibody; RF = rheumatoid factor

Source: Vivino FB. Sjogren's syndrome: a disease in evolution. *Medscape Rheumatology.* 2004;5:1-8.

Although the AECG criteria for Sjögren's disease have been validated in prospective studies, this classifications scheme is frequently criticized for the inclusion of symptoms as two major categories in the diagnostic algorithm. This criticism stems from the observation that the correlation between severity of ocular and oral symptoms and that of ocular and oral signs is often poor.[8] Additionally, the alternative tests proposed to document objective evidence of dry eyes (e.g. Schirmer's vs. vital dye staining) and dry mouth have different sensitivities and specificities and are, therefore, not diagnostically equivalent. Finally, some of the proposed studies (e.g. salivary scintigraphy) are not yet standardized and results may vary from center to center.

In an effort to create more robust diagnostic guidelines with higher specificity for Sjögren's disease (thereby minimizing the chance of exposing non-Sjögren's disease patients to the risks of biologics in clinical trials for the treatment of Sjögren's disease), the NIH-funded Sjögren's International Collaborative Clinical Alliance (SICCA) recruited patients with Sjögren's disease-like complaints or findings (N=1618) and published their own guidelines in 2012 based solely on objective criteria. The system defined Sjögren's disease as the presence of at least two of the following criteria: (1) positive serum autoantibodies (anti-Sjögren's syndrome-A [anti-SSA] and/or anti-Sjögren's syndrome-B [anti-SSB], or rheumatoid factor [RF] and antinuclear antibodies [ANA]); (2) positive minor labial salivary biopsy; and (3) keratoconjunctivitis sicca (KCS) as defined by fluorescein

Table III-2. American European Consensus Group Criteria for Diagnosis of Sjögren's Disease

1. Ocular symptoms (any 1 of 3)
   Dry eyes >3 months
   Tear use > tid
   Foreign body sensation in eyes
2. Oral symptoms (1 of 3)
   Dry mouth > 3 months
   Swollen salivary glands
   Need liquids to swallow/chew food
3. Ocular signs (1 of 2)
   Unanesthetized Schirmer's $\leq$ 5mm/5min (either eye)
   Positive vital dye staining (rose bengal, fluorescein, lissamine green)
   van Bijsterveld score $\geq$ 4*
4. Oral signs (1of 3)
   Abnormal salivary scintigraphy
   Abnormal parotid sialography
   Abnormal sialometry (unstimulated salivary flow $\leq$ 0.1ml /min)
5. Positive lip biopsy
   Focal lymphocytic sialadenitis (focus score $\geq$ 1 / 4mm^2)
6. Positive Anti-SSA and /or SSB antibodies

- Exclusions: hepatitis C, graft vs. host disease, anticholinergic medications, HIV, head/neck irradiation, pre-existing lymphoma, sarcoidosis.
- Diagnosis of 1° Sjögren's disease requires 4 of 6 criteria including # 5 or 6.
- Diagnosis of 2° Sjögren's disease requires established connective tissue disease, plus one sicca symptom (#1 or 2) plus 2 of 3 objective tests for dry eyes and mouth (#3-5).
- Diagnosis of Sjögren's disease can be made in patients who have no sicca symptoms if 3 of 4 objective criteria are fulfilled (#3-6).

* Van Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol*. 1969;82:10-4.

Source: Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. *Ann Rheum Dis.2002;*61:554-8.

and lissamine green ocular surface staining score (OSS).[8] (Table III-3)

The SICCA registry included adults with at least one of the following: dry eye symptoms, dry mouth symptoms, bilateral parotid enlargement, increasing dental caries, a Sjögren's disease diagnosis, or elevated titers of ANA, RF, anti-SSA, or anti-SSB antibodies. Analyses of this cohort using ACR criteria confirmed the variability of patient presentations consistent with Sjögren's disease. Among patients who met the criteria for Sjögren's disease (N=515), 60% (n=309) had all three findings: evidence of serum autoantibodies, ocular findings, and oral findings. However, 40% only had two: antibodies plus ocular findings but without oral signs (15% or n=76); antibodies plus oral findings but without ocular signs (8% or n=40); or oral and ocular signs but without antibodies (17% or n=90). Interestingly, a great number of patients within the SICCA registry met only one Sjögren's disease criterion (n=405), including 260 individuals with severe ocular staining (OSS $\geq$ 4). These patients represent a subset of non-Sjögren's disease patients with severe DED.[1] The underlying pathogenesis of this subset remains unknown.

Table III-3. American College of Rheumatology Preliminary Criteria for the Classification of Sjögren's Disease

1. Serologic: +SSA or SSB or +RF (any titer)/ANA $\geq$1:320
2. Histologic: +Biopsy = Focal lymphocytic sialadenitis (focus score $\geq$1/ 4mm^2) (same as AECG)
3. Keratoconjuctivitis sicca: +Ocular Surface Staining score* $\geq$ 3 either eye using fluorescein and lissamine green

- Exclusions: IgG-4 syndrome; otherwise same as AECG
- Diagnosis of Sjögren's disease requires fulfillment of 2 of 3 objective tests for classification as SS†

* Whitcher JP, Shiboski CH, Shiboski SC, et al. for the Sjogren's International Collaborative Clinical Alliance (SICCA) Research Groups. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjogren's Syndrome International Registry. *Am J Ophthalmol*. 2010;149:405-15.

† No distinction made between primary and secondary Sjogren's.

Source: Shiboski S, Shiboski C, Criswell L, et al. for the Sjogren's International Collaborative Clinical Alliance (SICCA) Research Groups. American College of Rheumatology classification criteria for Sjogren's syndrome: a data driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance Cohort. *Arthritis Care Res*. 2012; 64:475-87.

Both sets of criteria—the AECG and ACR/SICCA—are widely used with an approximate sensitivity and specificity of 90-95%, and both offer reasonable albeit imperfect reliability.[1,8,10] Interestingly, when both criteria were applied to the same patient group, the level of agreement was approximately 80%.[10] Since considerable overlap in testing requirements exists, clinicians may choose to apply both sets of criteria in order to extend their diagnostic capability. Recently, an international consensus committee was formed to develop a new hybrid model utilizing both the AECG and ACR-SICCA criteria. The diagnostic dilemma should ease as understanding of the pathologic basis of Sjögren's disease evolves and diagnostic tools based on pathogenesis become available.[10] One such test, the new multi-antibody blood test called Sjö™, was approved by the US FDA in 2013.[11] The Sjö™ test detects three novel serum autoantibodies that may be early biomarkers for Sjögren's disease. Clinical trials evaluating the place of Sjö™ in Sjögren's disease diagnosis are ongoing.

A. Epidemiology

Estimates of Sjögren's disease prevalence are complicated by lack of consensus around diagnostic criteria and lack of a single, well-accepted test for the disease. Estimated prevalence within the general population has been reported as 0.1-3% in the US and, similarly, 0.5-1% in Europe.[12,13] Thus, approximately 2 to 4 million individuals in the US have Sjögren's disease, many of whom remain undiagnosed.[14] Studies suggest that Sjögren's disease may represent at least 10% of clinically significant aqueous deficient DED cases.[12] A prospective study by Liew and coworkers demonstrated that a diagnosis of Sjögren's disease could be made in 11.6% of patients with at least 6 months of symptomatic DED with the following ocular findings: unanesthetized Schimer test $\leq$7 mm, corneal fluorescein staining score $\geq$4 (National Eye Institute Scale), and moderate-to-severe symptom score on the modified Ocular Comfort Index questionnaire.[12] The authors concluded that this figure is likely an underestimate of prevalence within the general population, as no salivary gland assessments were included in their protocol.

Sjögren's disease predominantly affects women 40 to 55 years of age. The female-to-male ratio is approximately 9:1; other estimates suggest 20:1.[14,15] However, as disease awareness and knowledge of diagnostic tests and criteria improves among providers, cases are identified among younger women, more and more men and, pediatric patients as well. Among primary autoimmune conditions, Sjögren's disease is considered to be second in prevalence only to RA.[16,17] Approximately 60% of Sjögren's disease cases are secondary to other autoimmune disorders.[14]

B. Presentations and Morbidity: Ocular Signs and Symptoms

Among patients with dry eye who present to an eyecare provider, suspicion of Sjögren's disease generally arises when the patient's dry eye signs or symptoms are severe, the patient is a middle-aged female, and/or the characteristic extraocular findings—dry mouth, fatigue, joint pain, and suspected or confirmed autoimmunity—are present. As a systemic disease, Sjögren's has the potential to affect nearly every organ system in the body.[14] Here we review common and less common manifestations of Sjögren's disease.

Dry eye is the most common ocular presentation of Sjögren's disease.[14] Dry eye associated with Sjögren's disease tends to be relatively severe; otherwise ocular manifestations associated with Sjögren's disease may be difficult to distinguish from other forms of aqueous deficient DED. Patients may complain of ocular itching, stinging, grittiness, soreness, photosensitivity, glare, erythema, discharge, decreased visual acuity, or visual blurring. Symptoms may be worse in low humidity environments, such as air conditioned rooms or dry climates, with smoke exposure, or when taking anticholinergic medications.[14]

Sjögren's disease-related DED is a form of aqueous deficient DED, although MGD may also be present.[18] Ocular surface inflammation is commonly seen in Sjögren's disease patients and may be severe. However, clinical inflammation is minimal or absent in some Sjögren's disease patients. (Inflammation, therefore, is an unreliable marker for Sjögren's disease, as many patients with DED unrelated to Sjögren's disease have significant ocular surface inflammation.) Due to the overall severity of ocular involvement, Sjögren's disease patients are at a higher risk for sight-threatening corneal involvement compared with non-Sjögren's disease patients, although comparative studies demonstrating this are lacking.

Due to a deficiency of aqueous tear fluid and inflammation-induced alterations in mucin production, thick rope-like discharge may be observed in the inner canthus of some eyes with Sjögren's disease.[14,18] Corneal epithelial erosions, corneal ulceration, and, in severe cases, corneal perforation requiring corneal transplant may occur.[14] Infectious complications such as bacterial conjunctivitis, keratitis, and blepharitis may also be present. In a retrospective study of patients with primary Sjögren's disease treated between 1999 and 2013 at Wilmer Eye Institute (N=183), 13% (n=23) had sight-threatening ocular involvement including corneal ulceration, corneal perforation, cicatrizing conjunctivitis, uveitis, optic neuritis, scleritis, or retinal vasculitis.[19] Serious ocular involvement was associated with an increased risk for systemic manifestations of Sjögren's disease.

Among Sjögren's disease patients, there is considerable variation in the degree of ocular involvement and response to treatment. Although severity may fluctuate, a majority of Sjögren's disease patients have some level of chronic DED throughout life. More rarely, patients may have periods of severe dry eye interspersed with periods of milder or even seemingly remittent signs and

symptoms, depending upon their general health or ambient environmental challenges.

C. Oral Manifestations

Patients with oral manifestations of Sjögren's disease may present with xerostomia (dry mouth) or less obvious complaints such as difficulty eating dry food, unusual taste, or difficulty speaking and swallowing or swelling of the salivary glands. With advanced oral dryness, patients may have diminished levels of pooling saliva, drying and wrinkling of the oral mucosa, and sticking of the tongue to the roof of the mouth producing a clicking sound during speech. Tongue manifestations secondary to Sjögren's disease may include redness, lobulation, depapillation, and, in advanced cases, fissuring.[14]

Complications of untreated xerostomia may include accelerated caries, loss of dentition, poorly fitting dentures, recurrent oral candidiasis, sialolithiasis (salivary stones), acute bacterial sialadenitis (usually due to *Staphylococcus, Streptococcus* or gram negative bacteria), dysphagia leading to weight loss and malnutrition, and chronic sleep disturbance.[14]

Sjögren's disease patients are also at risk for the development of chronic erythematous candidiasis, which can be painful and difficult to treat. Symptoms of chronic erythematous candidiasis include stomatopyrosis (burning of the mouth and tongue) and intolerance to spicy foods. Physical findings include atrophy of filiform papillae, mucosal erythema, and angular cheilitis.[20]

D. Other Xeroses

Xeroses beyond the eyes and mouth can significantly compromise quality of life in patients with Sjögren's disease; however, these features of the disease tend to receive less clinical attention. Dry skin (xeroderma) due to impaired sweating is common among Sjögren's patients. Patients may complain of dryness, pruritis, or prickly sensations, and they may observe rough and scaling skin.[21] In addition, deficient glandular secretions of the upper respiratory track can cause dryness of the nose, throat, and trachea (xerotrachea), leading to hoarseness and a chronic, nonproductive cough.[14] Vaginal dryness (vaginitis sicca) may affect female Sjögren's disease patients and may cause dyspareunia and itching.[14] Since most Sjögren's disease patients are peri- or postmenopausal females, symptoms of vaginal and vulvar dryness may relate to hormonal changes, autoimmune dysfunction, or both and can be overlooked as a symptom of Sjögren's disease.

E. Systemic or Extraglandular Involvement

Systemic and/or extraglandular involvement is frequently present among patients with Sjögren's disease. (Table III-4) Some studies suggest that upwards of 50% of Sjögren's disease patients develop extraglandular manifestations of the disease, most commonly articular, pulmonary, and neurologic.[22,23] Others show that when hematologic and dermatologic findings are excluded, extraglandular involvement is fairly low, particularly as it pertains to thyroid, kidney, liver, and perhaps neurologic complications.[15] Sjögren's can also be associated with a variety of other autoimmune diseases, including autoimmune thyroiditis, celiac sprue, chronic active autoimmune hepatitis, interstitial cystitis, and primary biliary cirrhosis. Clinicians should be vigilant for systemic involvement in all Sjögren's disease patients and should keep a low threshold for patient referral when a new or recurrent systemic manifestation is suspected.

Systemic complications may occur for a variety of reasons, including exocrine dysfunction (eg, recurrent bronchitis or sinusitis), extraglandular spread of lymphocytic infiltration (eg, interstitial lung disease), or nervous system dysfunction (eg, peripheral neuropathy). Other manifestations may be a consequence of hematologic or lymphoproliferative complications (eg, lymphomas). Some extraglandular manifestations of Sjögren's disease resemble those seen in related autoimmune conditions such as SLE; these include arthralgia and myalgia with or without objective signs of arthritis, myositis, and Raynaud's syndrome.

Hematologic manifestations include anemia, thrombocytopenia, and leukopenia, the last of which raises concern about vulnerability to infection.[18] Gastrointestinal complications include difficulty swallowing, heartburn, autoimmune pancreatitis, autoimmune liver disease, chronic bloating with diarrhea due to small bowel bacterial overgrowth syndrome (similar to that seen in SLE), abdominal angina (due to medium vessel vasculitis), and constipation. The most common Sjögren's disease-related renal disorder is interstitial nephritis due to lymphocytic infiltration; glomerular nephritis and renal tubular acidosis types I and II can also result.

Sjögren's disease patients are at risk for a range of pulmonary complications. Impaired moisture-production in the airways (xerotrachea) typically manifests as a chronic, dry cough. The combination of dryness and impaired ciliary function places patients at risk for recurrent bronchitis and pneumonia. Lymphocytic infiltration of the pulmonary interstitium can lead to interstitial pneumonitis, which, in early stages, can mimic pneumonia. As it advances, patients develop chronic coughing and shortness of breath on exertion. If undiagnosed and untreated, permanent scarring of the lungs (pulmonary fibrosis)—a very serious complication—may develop. Bronchiolitis obliterans, a lymphocytic infiltration of the small airway walls, typically presents as wheezing and shortness of breath. Coughing and sputum production may signal the development of bronchiectasis, a condition characterized by airway dilatation and bacterial colonization.

In addition to xeroderma, dermatologic manifestations of Sjögren's disease include hives, sun-induced rashes, and various types of maculopapular rashes. The most severe form of dermatologic involvement is leukocytoclastic vasculitis. This typically presents as petechiae or palpable or

Table III-4. Common Extraocular and Extraoral Manifestations of Sjögren's Disease

Constitutional
Fatigue
Malaise
Fevers
Rheumatologic
Arthralgias
Polyarthritis
Myalgias
Raynaud's phenomena
Skin/ Mucous Membranes
Xeroderma (dry skin)
Purpura (leukocytoclastic vasculitis or hypergammaglobulinemic purpura)
Urticaria
Mouth sores
Candida—oral and vaginal
Vaginitis sicca (vaginal dryness)
Hematologic/ Neoplastic
Leukopenia
Lymphopenia
Neutropenia
Anemia
Thrombocytopenia
Cryoglobulinemia
Lymphadenopathy
Lymphoma, most commonly non-Hodgkin's B-cell
Gastrointestinal
Dysphagia associated with xerostomia
Esophageal dysmotility
Esophageal webs
Gastroesophageal reflux
Atrophic gastritis
Autoimmune pancreatitis
Hepatitis
Constipation
Otolaryngology
Epistaxis
Otitis media
Hearing Loss
Recurrent sinusitis
Laryngeal tracheal reflux
Renal/ Urinary
Interstitial nephritis
Renal tubular acidosis, types I and II
Glomerulonephritis
Pulmonary
Xerotrachea
Interstitial pneumonitis
Pulmonary fibrosis
Recurrent bronchitis and pneumonia
Bronchiectasis
Bronchiolitis obliterans
Lung nodules
Neuromuscular
Peripheral neuropathy
Mononeuritis multiplex
Demyelinating disease
Cranial neuropathy
Autonomic neuropathy
Cognitive dysfunction
Myositis
Pregnancy-related
Fetal complications, eg, congenital heart block

Sources: Fox RI, Saito I. Sjogren's syndrome. In: Hertl M, ed. *Autoimmune Diseases of the Skin*. Second Revison. New York, NY: SpringerWein; 2005; Derk CT, Vivino FB. A primary care approach to Sjogren's syndrome. *Postgraduate Medicine*. 2004 ;116:49-65.

nonpalpable purpura on the distal lower extremities and is the result of neutrophilic infiltration of small blood vessels of the skin.[18,21]

Common Sjögren's disease-related neurologic disorders include headache, cognitive dysfunction involving memory and concentration (sometimes referred to as brain fog), and mood disorders.[24] Demyelinating disease similar to multiple sclerosis has also been reported in association with Sjögren's disease. Patients may also develop a wide variety of peripheral neuropathic conditions, which may manifest as pain, sensory or motor impairment, ataxia, or autonomic dysfunction.[25] One of the most common extraglandular manifestations of Sjögren's disease is fatigue, ranging in severity from mild to debilitating. Fatigue may be the result of an inflammatory process, sleep disturbance, hormonal imbalance (eg, thyroid disorder), vitamin deficiency or other cause.[18,26] Fatigue may manifest as a general tiredness throughout the day or waning energy by afternoon or evening compromising the ability to complete a full workday. Midday fatigue may relate in part increasing dry eye symptoms—eg, ocular surface irritability, light sensitivity, more blinking—over the course of the day, which can impede work efficiency and leave patients feeling tired. Fatigue may also contribute to depressed mood, a common finding among patients with Sjögren's disease.

Pregnancy among Sjögren's disease patients may occasionally be complicated by miscarriage or thrombosis; fetal risk for congenital heart block is increased.[18]

F. Lymphoproliferative/Myeloproliferative

Among autoimmune diseases, Sjögren's disease has the highest incidence of associated benign and malignant lymphoproliferative disorders.[27] Lymphoproliferative complications of Sjögren's disease include lymphadenopathy,

enlarged salivary glands, pulmonary infiltrates, and splenomegaly.[14] Additionally, between 1% and 10% of patients with primary Sjögren's disease develop non-Hodgkin's B-cell lymphomas, a rate up to 40 times that of unaffected peers.[18,22,27] The most common cell types are mucosa associated lymphoid tissue (aka marginal zone B cell) lymphomas. Lymphoma originating in parotid and submandibular glands is especially common.[18] Although the etiopathogenesis of Sjögren's disease-related lymphoma is not known, several risk factors have been identified, including severe exocrine gland involvement, parotid swelling, splenomegaly, leukocytoclastic vasculitis, hypocomplementemia, and cryoglobulinemia.[22,27] A recent report documented a strong association between a mutation in the A20 (TNFAIP3) tumor suppressor gene and mucosa associated lymphoid tissue lymphomas in primary Sjögren's patients.[28]

Rare reports of other hematologic malignancies among Sjögren's disease patients include multiple myeloma, primary nodal plasmacytoma, lymphocytic leukemia, and multicentric Castelman's disease.[27] Mortality among patients with primary Sjögren's disease is slightly higher than that of the general population due to Sjögren's disease patients' increased risk for hematologic malignancy.[22]

G. Etiopathogenesis

The etiopathogenesis of Sjögren's disease has been recently reviewed.[29] Genes, hormones, and environmental factors (eg, infection with a sialotropic virus) may all play a role. Animal models of Sjögren's disease suggest that disease susceptibility may be multigenic, meaning that heterogeneous combinations of genetic polymorphisms may contribute to the development or predisposition for development of Sjögren's disease. This is evidenced by the array of presentations and findings among Sjögren's disease patients as well as the variable presence of autoantibodies, which serve not only as markers but also likely play a role in pathogenesis.[30]

A leading pathogenic theory related to Sjögren's disease (as well as other autoimmune diseases) involves a combination of genetic and infectious factors. Simply stated, the idea is that an immunogenetically susceptible individual who encounters a certain virus or bacterium mounts an immune attack against the pathogen; however, because the antigen toward which the immune attack is directed bears a strong resemblance to a human cellular epitope—such as a bit of ribonucleic acid (RNA) or a cellular heat shock protein—the immune system misdirects its efforts and harms human tissue rather than the invader. Associations of Sjögren's disease with Epstein-Barr virus (EBV), hepatitis C virus, human T-cell leukemia virus type 1 (HTLV-1), and *Helicobacter pylori* have been suggested, but proof is lacking.[31,32]

Hormonal changes during menopause may also play a role in the development of Sjögren's disease. Estrogen is protective of exocrine cells and indirectly of secretory acinar cells; therefore, declining levels leave exocrine cells vulnerable to dysfunction and apoptotic death. Sjögren's disease development may relate to a breakdown in autotolerance that occurs when cell turnover is high and debris-clearing mechanisms overwhelmed.[33] Baseline DED-associated ocular surface inflammation (related to computer overuse, medications or other non-Sjögren's disease factors) may raise the cell death toll, causing fragment release and thus contributing to an overall state of autoimmune susceptibility. Indeed, studies have demonstrated that exocrine glands in Sjögren's disease not only suffer immune insult but also perpetuate the cycle.[31]

One of the fastest moving fields in medical research surrounds the role of the normal human flora in maintaining health and preventing disease. Commensal bacteria in the gut may play a role in immune tolerance, while alterations in gut flora may contribute to pathogenesis in SLE, Sjögren's disease, and other common systemic autoimmune disorders.[34]

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IV. DIAGNOSIS OF DED

A. Symptoms

DED is usually accompanied by characteristic symptoms of discomfort and/or visual disturbance. (Table IV-1) The ocular discomfort may be described as irritation, burning, grittiness, foreign body sensation, itching, or ocular fatigue.[1] A number of questionnaires have been developed to catalogue and quantify the degree of discomfort; evidence shows that some questionnaires are better for detecting evaporative versus aqueous deficient DED.[2,3]

Disturbance of visual function is most often described as blurred vision, typically experienced when the patient is reading or concentrating on computer work.[4] Symptoms are typically aggravated by prolonged near work or environmental conditions such as a dry or drafty milieu and may be transiently improved with topical lubricants.[5] Paradoxically, patients with early DED may retain good ocular sensitivity and experience greater symptoms than those with more severe DED, in which corneal sensation is decreased. As a result, the patient may experience less severe symptoms despite greater signs of DED.[6-8]

Table IV-1. Dry Eye Disease (Sjögren's Disease and non-Sjögren's Disease) Symptoms *†

Irritation
Burning
Grittiness
Foreign body sensation
Itchiness
Ocular fatigue
Blurred vision (particularly with reading or concentrated work at display terminal)
Temporary relief with topical lubricants
Aggravating factors
Prolonged near work
Low humidity
Drafty air currents

* Symptoms do not necessarily correlate with severity.

† Sjögren's disease patients may have more severe or treatment-recalcitrant symptoms compared with non-Sjögren's disease dry eye patients.

Recent studies have identified patients with confirmed DED who lack symptoms; such patients present a unique challenge to the clinician.[9] Sjögren's disease-associated DED manifests itself in the same way as non-Sjögren's disease DED, but the severity of symptoms and signs is often greater, and the disease is often more difficult to treat effectively.

B. DED Examination and Testing

Clinical evaluation of the patient with DED symptoms must include examination of the eyelids, tear film, tear film composition, and integrity of the ocular surface. Testing for the presence of DED has traditionally involved determining tear film stability and tear volume, as well as evaluating the health of the ocular surface by use of topically applied vital stains.[1] Recent advances in technology have enabled more precise testing of tear film stability, volume, and composition.[4,5]

C. External Examination

The eyelid margin is a particularly important area to examine with the slit lamp, as MGD is the most common cause of evaporative DED. It is important to determine whether MGD is present—either alone or in combination with aqueous deficient DED—in any given patient.[10,11] This is especially true in patients with Sjögren's disease, as recent studies have confirmed an association between Sjögren's disease and MGD as well as aqueous deficient DED.[12]

Erythema of the posterior lid margin with dilation of the vessels occurs in acute inflammatory MGD and may be accompanied by telangiectasia of the lid margin in chronic MGD. Meibomian gland orifices should be assessed for plugging and inspissation of secretions, and the expressibility of the glands should be evaluated.[13,14]

D. Tear Quantity and Quality

Determination of tear film stability is an important early step in evaluating any form of DED. Tear film instability is a hallmark of DED and is reflected in both tear film breakup time (TFBUT) and in composition of the tear fluid.[4]

Measured in seconds, TFBUT denotes how long the tear film remains intact after blink and is the most widely used measure of tear film stability. The test is performed by adding dilute fluorescein dye to the tear film and observing with the slit lamp under cobalt blue filtered light. The traditional threshold value for diagnosis of DED has been TFBUT less than 10 seconds, but recent studies suggest a shorter TFBUT ($<$ 5 seconds) when instilling small volumes of fluorescein solution has more specificity but less sensitivity.[1,15,16] Recent advances in technology allow non-invasive measurement of tear film stability with rapid and reproducible optical methods.[17,18]

Measurement of tear volume and change in tear volume have traditionally been performed using the Schirmer test, in which paper strips are applied over the lower eyelid margin for 5 minutes in eyes that either have or have not been anesthetized.[1] Normal wetting of the paper strip is 10 mm or more in 5 minutes. Diagnostic accuracy increases as the threshold is reduced to 5 mm or even 3 mm, but this risks missing patients with early or mild DED. The AECG considers $\leq$ 5 mm of wetting in 5 minutes in a Schirmer test without anesthetic as a diagnostic feature of Sjögren's disease.[19] Documentation of the above findings is only required in one eye for a positive test.

Use of the Schirmer strip following instillation of topical anesthesia usually reduces the risk of measuring reflex tearing, but liquid from the topical anesthetic can alter the test result, and many clinicians remove the added volume with the corner of a tissue prior to Schirmer strip placement.[1,10] Recent studies have shown that, particularly with mild DED, the accuracy of the Schirmer test is equivocal and not diagnostic of evaporative DED.[20-22] A recent study also indicated that Schirmer testing was not very efficient in diagnosis of Sjögren's disease-associated DED, although a second study indicated that use of a combination of Schirmer test with phenol red test increased accuracy.[10,23]

The phenol red thread test also measures tear volume; it requires less time and is associated with less reflex secretion than Schirmer testing. The normal value is 10 mm or greater per 15 seconds.[1,23]

Measurement of tear volume can now be done with advanced technology that measures the curvature of the inferior tear meniscus by reflectometry or by optical coherence tomography (OCT).[24-27] Schirmer testing is inexpensive and readily available, but newer methods that are more accurate and more comfortable to the patient may eventually replace the Schirmer test.[28]

E. Tear Flow and Turnover

The rate of tear flow can be determined by dilution methods after instillation of an appropriate marker dye. In research settings, fluorophotometric measurement of the rate of decay in fluorescence of instilled fluorescein has been used; however, the necessary instrumentation is not generally available in primary care settings.[1,29,30] An alternative approach to determining tear turnover is to use sequential sampling of the fluorescein stained tear film by application of Schirmer strips over a 20-minute time period with assessment of dilution of the dye in the strip.[31]

F. Tear Composition

The determination of tear osmolarity as a characteristic feature of DED was extensively studied by Farris and coworkers in the 1970s.[32] Tomlinson and coworkers performed an extensive meta-analysis of published reports of osmolarity testing and determined that 316 mOsm/L was an effective diagnostic cutoff value, but the population studied probably reflected more severely diseased patients.[33] A more recent study of a larger population of patients with mild DED suggested that 305 mOsm/L was a more accurate threshold value.[34,35] A study more representative of the

Figure IV-1. TearLab Osmometer for point of care testing. Point-of-Care testing of osmolarity provides early diagnostic and staging information. Courtesy of TearLab, Inc.

entire spectrum of DED recommended ≥308 mOsm/L as the most sensitive diagnostic referent value, especially when there is variability between eyes or variability over time.[36,37] Normal eyes without DED demonstrate a very stable osmolarity, both between eyes and in the same eye over time. In contrast, patients with DED have considerable variability in osmolarity, both between eyes and over time in the same eye.[28,37]

"Lab-on-a-chip" technology has allowed rapid point-of-care determination of osmolarity in the clinical setting with an FDA approved device.[4,21,36] Several studies have indicated that tear osmolarity is a valuable method of diagnosing DED across the severity spectrum of the disease, while others have raised questions about its clinical utility.[21,34,36-39] The present recommendation with use of the TearLab Osmometer is to test both eyes. If the osmolarity in either eye is greater than 308 mOsm/L a diagnosis of DED can be made. If the measurement is below 308 mOsm/L but the suspicion for DED is high, repeated measurements can be taken at different clinic visits. It is important to test for osmolarity *before* drops of any sort are instilled. Osmolarity testing does not distinguish between evaporative and aqueous deficient DED. The lab-on-a-chip osmometer should be housed at room temperature in a temperature-controlled room away from radiators or air conditioning vents and periodic calibration with the provided standard solutions should be done. (Figure IV-1)

G. Tear Proteins

Changes occur in many protein constituents of the tear fluid in DED. Some components are decreased (eg, lysozyme, lactoferrin, Mucin 5AC [MUC5AC]) and others are increased (eg, matrix metalloproteinase, some cytokines).[1,40] Measuring tear protein concentrations is difficult due to small test volumes and complicated methods for measuring the proteins. Nonetheless, in-office testing of selected proteins with relevance to DED is possible. Matrix metalloproteinase-9 (MMP9) is one such protein that is associated with ocular surface inflammation.[41,42] A semiquantitative commercial immunoassay to measure tear MMP9 has been approved in Europe, Canada, and the United States. The RPS InflammaDry® test is a semiquantitative method that identifies MMP9 levels greater than 40 ng/mL.[43] (Figure IV-2)

Published studies have found good sensitivity and specificity detecting DED-associated inflammation, but the test can be positive in any condition associated with ocular surface inflammation, including allergy. Its most appropriate use may be in detecting those DED-related conditions associated with inflammation, including Sjögren's disease.[43,44]

H. Ocular Surface Dye Staining

Ocular surface staining is a hallmark of DED and is usually associated with moderate to severe disease that has resulted in damage to the ocular surface.[1] Ocular surface staining with any vital dye can be utilized to document the ocular component of the modified AECG criteria for the presence of Sjögren's disease.[19]

The dye most frequently used to detect staining of the ocular surface is fluorescein, which stains both cornea and conjunctiva. Instilled as a drop of 0.5% to 1% solution or by wetting a fluorescein impregnated strip, the dye stains damaged surface cells and adherent mucus. Fluorescein staining is most easily seen on the cornea at the slit lamp biomicroscope using cobalt blue light and is optimal at 2 to 2.5 minutes following instillation. The intensity of corneal staining can be enhanced by using a yellow barrier filter (Wratten #11) before the ocular examination. The yellow filter also helps in detecting conjunctival staining.[45]

The classical staining pattern is an interpalpebral band across the center of the cornea and nasal and temporal conjunctival surface, but analysis of recent clinical trials has shown that corneal staining intensity typically occurs as follows: inferior cornea > nasal cornea > central = temporal cornea > superior cornea.[46]

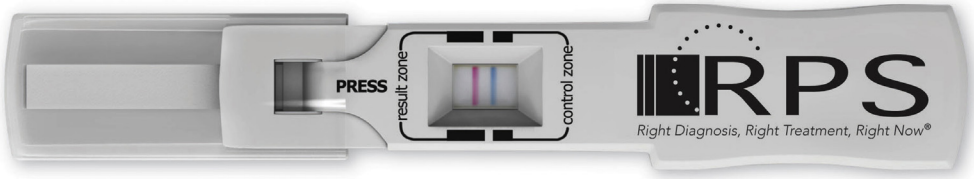

Figure IV-2. RPS InflammaDry MMP9 test strip for point of care testing. Point-of-Care testing for presence of MMP-9 allows determination of presence of inflammation. Courtesy of RPS, Inc.

Table IV-2. Dry Eye Disease (Sjögren's Disease and non-Sjögren's Disease) Tests

Test	Measure of	Units measured	Normal	Abnormal	Notes
Fluorescein Tear Break Up Time (FTBUT)	Tear film stability	Seconds to break up after blink	10-20	<10 possibly abnormal; <5 abnormal	
Tear film stability analysis system (TSAS)	Tear film stability	Time from complete blink to distortion of image			
Tear thinning time by Keratography	Tear film stability				
Schirmer basic secretion test, anesthetized	Tear volume	mm over 5 minutes	>5	<5	Assesses lacrimal gland function
Schirmer test, unanesthetized (Schirmer I)	Tear volume	mm over 5 minutes	>5	< or = 5	Not diagnostic of evaporative
Reflectometry/ Tear meniscus height	Tear volume	mm curvature of inferior tear meniscus	>0.2 mm (range 0.1 − 0.6 mm)	Scanty or absent tear meniscus indicative of ADDE	
OCT	Tear volume				
Phenol red thread test	Tear volume	mm/ 15 seconds	>10	<10	Less reflex tearing vs. Schirmers
Fluorescein fluorometry assessment	Tear flow				Limited availability in clinical setting
Osmometry	Tear osmolarity/ lacrimal gland function	mOsm/L	<305 mOsm/L	>308 mOsm/L	Does not distinguish between evaporative and ADDE
MMP-9 test	Ocular surface inflammation (tear MMP-9 level)	+ or − (positive = > or = 40 ng/mL)	- (negative)	+ (positive)	Nonspecific for surface inflammation
Fluorescein staining- von Bjisterveld (AECS)	Ocular surface staining; microepithelial defects; mucus deficiency	Score of 0 − 9	No staining or < or = 3	>4	Stains cornea and conjunctiva; May reveal micropunctate dots, macropunctate spots, coalescent staining, frank epithelial defects
Rose Bengal staining	Staining of non mucin-coated epithelium	Score 0 - 9	No staining visible	Micropunctate staining	Increased temporal conjunctiva staining may indicate Sjogren's; may sting on installation; interferes with herpes culture
Lissamine green staining	Staining of non mucin-coated epithelium	Score 0 - 9	No staining visible	Micropunctate staining	Use adequate volume; better tolerated than rose bengal
Meibography	Meibomian gland structure and number				

Table IV-2. continues on the following page

Table IV-2. Dry Eye Disease (Sjögren's Disease and non-Sjögren's Disease) Tests *(continued from previous page)*

Test	Measure of	Units measured	Normal	Abnormal	Notes
In vivo confocal microscopy	Meibomian gland structure and inflammatory infiltrate				
En-face spectral domain ocular CT	Meibomian gland structure and inflammatory infiltrate				
SSA or anti-Rho; SSB or anti-La; RF; ANA	Serum autoantibodies		Negative	Positive	Varying rates of sensitivity and specificity for SS

Several grading systems have been developed to quantify fluorescein stain. In the earliest system (described by von Bjisterveld) staining is graded from 0 to 3 in the cornea, nasal bulbar conjunctiva, and temporal bulbar conjunctiva, with a possible maximum score of 9 for each eye.[47] This is the scoring system recommended by the modified AECG, which requires a minimum score ≥ 4 to diagnose Sjögren's disease.[19] Early-stage staining patterns include micropunctate dots; progressive severity can lead to macropunctate spots, coalescent staining, or frank epithelial defects. Adherent mucus and filaments on the cornea also stain with fluorescein. When frank epithelial defects are present, fluorescein can penetrate into the stroma as a diffuse haze, obscuring detail of the other surface staining.

Other grading systems include the National Eye Institute/Industry Workshop scale, which evaluates the cornea in five sectors, with a scale of 0 to 3 in each sector for a combined maximum score of 15;[48] the Oxford System, which utilizes 5 grades including cornea and conjunctiva;[45] the Japanese Grading System, which evaluates each of the superior, central, and inferior regions of the cornea on a 0-3 scale or by area and density of staining;[49] and the SICCA OSS scale, which utilizes vital dyes and scores the areas of nasal bulbar conjunctiva, temporal bulbar conjunctiva, and cornea by counting dots of staining in each area on a 0-3 scale and adding them together. Additional points are added for areas of confluent staining, involvement of the pupils and ocular surface filaments for a maximum score of 12 in each eye. [50]

The SICCA OSS was recently developed by an international team of ophthalmologists in order to simplify and standardize ocular surface assessment and grading among patients with DED and suspected Sjögren's disease.[50] It uses lissamine green to stain the conjunctiva and fluorescein to stain the cornea, arriving at a grade between 0 to 12 for each eye depending on severity and extent of involvement. A score ≥ 3 in either eye represents a clinically significant abnormal OSS.

I. Rose Bengal

Rose bengal is a dye related to fluorescein but with a red color. Applied as a 0.5% or 1% solution to the conjunctival cul-de-sac, it stains both cornea and conjunctiva when there is altered mucin expression of the ocular surface epithelium or if adherent mucus is present (including filaments). The staining of the cornea is occasionally difficult to see, but the conjunctival staining is prominent, even with white light.

Some data suggest that increased staining of the temporal conjunctiva is a reliable indicator of Sjögren's disease-related DED, but the association may also be explained by increased severity of staining of the temporal conjunctiva due to the greater severity of Sjögren's disease-related DED.[51] Rose bengal stings upon instillation, and patients often do not tolerate the sensation. This stain can cause cells to be sensitive to infrared light,

and it is known to inhibit culture recovery of herpes simplex virus.[52]

J. Lissamine Green

Lissamine green is a food dye that stains the ocular surface in the same pattern as rose bengal but without the stinging sensation or possible damage to epithelial cells.[53] Instilled as a 1% solution, the optimal drop size is 10 microliters, and it is important to use adequate volume to elicit proper staining.[54] Staining is best viewed at the slit lamp under low illumination between 1 and 4 minutes following instillation and after several complete blinks. Interpretation and grading of the staining is the same as with rose bengal. Patient tolerance of application is much better than rose bengal.

K. Meibography and Proteomic Analysis

Meibography is now possible with new instrumentation that images the glandular structure and allows quantification of gland dropout.[55] *In vivo* confocal microscopy and en-face spectral domain ocular computed tomography have shown promising accuracy in identifying meibomian gland structure and adjacent inflammatory cell infiltration in MGD.[56,57]

Proteomic analysis has been applied to evaluation of tear proteins and may hold promise in providing diagnosis of DED.[58-60] To date, 1543 different proteins have been found in normal tears, and patterns of altered protein composition in DED have been identified.[60,61] Although the sophisticated equipment needed to perform proteomic testing is still limited to academic centers, there are reports of techniques applicable to the clinical setting.[61,62]

All of the traditional clinical tests for DED diagnosis are well described in the DEWS Report, along with analysis of the specificity, sensitivity, and predictive value of each test.[1] DED is a multifactorial disorder that requires evaluation of both symptoms and signs for diagnosis but with recognition that there is often only a weak correlation between symptoms and signs, particularly in patients with very mild or very severe disease. Multiple clinical tests may be needed to confirm the diagnosis, and variability between eyes and over time is to be expected, especially in patients with early or mild disease.[9,21] (Table IV-2)

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V. AN ALGORITHM FOR SJÖGREN'S DISEASE DIAGNOSIS

It is important for eyecare providers to maintain a high degree of suspicion of Sjögren's disease when evaluating DED patients so that referrals for Sjögren's disease evaluations can be made in a timely manner. Determining which DED patients should be referred for a Sjögren's disease work-up has historically been challenging. Because DED is highly prevalent, one can't simply refer all DED patients for a work-up. Referral for a rheumatology work-up should be considered in DED patients with any of the following: (1) a positive review of systems for extraocular involvement consistent with Sjögren's disease; (2) moderate-to-severe ocular surface findings; or (3) symptoms or signs refractory to standard treatment.

While the classic manifestations of Sjögren's disease are sicca symptoms (primarily dry eye and dry mouth), it is important to perform a thorough review of systems, as

this can help identify cases in which the probability of finding Sjögren's disease is high.

As discussed in Section III (Sjögren's Disease: The Disease State), patients with Sjögren's disease can have a wide variety of extraglandular symptoms—in addition to dry mouth, these may include dry nose, dry throat, chronic cough, dry skin, vaginal dryness, arthralgias, and fatigue.[1] A recent study found that the most common systemic symptoms in a cohort of Sjögren's disease patients involved the joints, lungs, skin, and peripheral nerves.[2] Another study reported that the presence of three symptoms (dry mouth, sore mouth, and dry eye) correctly classified 93% of cases and 97.7% of controls.[3] As a result, any DED patient with any systemic symptoms suggestive of Sjögren's disease, especially dry mouth or sore mouth, should be considered for a rheumatology work-up.

All patients with moderate-to-severe ocular surface damage due to DED should be considered for a Sjögren's disease work-up. One approach would be to refer all patients who fall into a DEWS dry eye severity level 3 or 4.[4] For example, those patients with Schirmer-without-anesthetic scores less than or equal to 5 mm/5 minutes should be referred for a work-up. In addition, patients with a moderate-severe degree of ocular surface staining (for example 2+ to 3+ staining of conjunctiva with lissamine green or rose bengal; or 2+ to 3+ fluorescein staining of the cornea according to the DEWS grading system), should also be worked up for Sjögren's disease.

Previous studies in the literature provide some guidance as to which DED patients would benefit from a rheumatology work-up based on the ocular surface exam. Caffery and colleagues found that the presence of temporal staining of the conjunctiva with rose bengal correlated with a diagnosis of Sjögren's disease.[5] The authors also found that temporal conjunctival staining with rose bengal and severity of dry mouth symptoms were the major factors in distinguishing primary Sjögren's disease patients from non-Sjögren's DED patients. In addition, in a prospective study, Liew and colleagues found that patients with Sjögren's disease had worse conjunctival lissamine green staining, corneal fluorescein staining, Schirmer test scores (with and without anesthetic), and total Ocular Surface Disease Index (OSDI) scores than DED patients without Sjögren's disease.[1] However, the authors did not find a correlation between temporal conjunctival lissamine green staining and a diagnosis of Sjögren's disease. Other studies have not found ocular surface tests useful in distinguishing Sjögren's disease-related from non-Sjögren's disease related DED. A small retrospective study found that TFBUT, Schirmer test, and corneal fluorescein staining did not correlate with a diagnosis of Sjögren's disease in a cohort of DED patients.[6]

New DED diagnostic tests, such as tear film OCT and tear osmolarity, have been evaluated for their ability to distinguish Sjögren's disease from non-Sjögren's DED. In a study by Qui and coworkers, which included 53 patients with Sjögren's disease, tear meniscus parameters measured by OCT were significantly lower in Sjögren's disease compared to non-Sjögren's disease aqueous deficient DED patients.[7] However, further larger studies are needed to evaluate the potential utility of OCT-tear film analysis in the selection of DED patients who have a high likelihood of having Sjögren's disease.

There have been conflicting results regarding the utility of tear osmolarity in diagnosing Sjögren's disease. Bunya and coworkers found an elevated mean tear osmolarity in 49 subjects with Sjögren's disease.[8] However, Szalai and coworkers did not find any significant difference in tear osmolarity between DED patients (which included Sjögren's disease patients) and controls, although this study's methodology has been criticized.[9,10]

Finally, a diagnosis of Sjögren's disease should be considered in any DED patient whose ocular surface disease is refractory to the full array of standard therapies, including physical measures, dietary modification, tear substitutes, topical corticosteroids, and topical cyclosporine. The time needed to ascertain treatment response can be expected to vary from patient to patient, as it depends upon disease severity at presentation, types and sequence of therapies prescribed, frequency and methods of monitoring used, and individual patient course. For some DED patients, "treatment refractory" may be an appropriate designation after only 6 to 8 months of unsuccessful therapy. For other patients, a longer time period may be warranted, especially considering that improvements related to topical cyclosporine can take several months to achieve. Once standard treatment options have been exhausted, patients experiencing continued ocular surface disease should be referred for a rheumatology work-up.

A. Current State of Antibody Testing for Sjögren's Disease

The presence of conventional autoantibodies—typically anti-SSA (also called anti-Ro), anti-SSB (also called anti-La), rheumatoid factor (RF), and anti-nuclear antibodies (ANA)—contributes to establishing the diagnosis. However, their usefulness is limited by low specificity and sensitivity, particularly low sensitivity at early stages of disease.

RF and ANA autoantibodies are associated with a range of autoimmune disorders; neither is highly specific nor sensitive for Sjögren's disease. Studies suggest that 36% to 74% of patients with Sjögren's disease have a positive test for RF; 59% to 85% are ANA-positive.[11]

Anti-Ro and anti-La are human autoantibodies that attach to distinct epitopes on nuclear or cytoplasmic RNA, creating Ro/La-RNA complexes. They may be detected in the serum, salivary secretions, and/or tear film of patients with Sjögren's disease and are thought to participate in the antigen-driven immune response that underlies Sjögren's disease pathogenesis.[12,13] Anti-Ro and anti-La are the most prevalent and the most disease specific among conventional serum biomarkers.[12] However, depending on the method employed for testing, serum anti-Ro and anti-La is detectable among only 33% to 74% and 23% to 52% of primary Sjögren's disease patients, respectively. Thus, sensitivity is

low; between 26% and 67% of Sjögren's disease patients do not have detectable levels of these biomarkers and would go undiagnosed without additional assessments.[11] Among patients with secondary Sjögren's disease, sensitivity is even lower: only 5% to 15% of patients with Sjögren's disease secondary to RA and approximately 40% of patients with Sjögren's disease secondary to SLE have detectable anti-La and/or anti-Ro autoantibodies.[12]

Current ACR and AECG diagnostic criteria for Sjögren's disease utilize anti-Ro and anti-La antibodies.[14] Detection of anti-Ro and/or anti-La antibodies is correlated with longer disease duration, higher lymphocytic infiltration of the salivary glands, and a higher rate of extraglandular disease.[11,12] Some studies have also shown that anti-Ro and anti-La positivity correlate with greater subjective and objective ocular surface involvement.[11]

Although conventional serologic markers for Sjögren's disease—anti-Ro, anti-La, RF, and ANA—are frequently relied upon for diagnosis, the diagnostic process would be greatly helped by the discovery of serological markers that appear earlier in the course of disease. Recent identification of target-organ specific serological markers may expedite the diagnosis of Sjögren's disease in the future. These markers have the potential to improve the sensitivity and specificity of detection of Sjögren's disease, particularly in early-stage patients.

B. Novel Autoantibiodies

The initial discovery of novel antibodies occurred in a mouse model for Sjögren's disease.[15] Shen and colleagues studied autoantibody patterns in interleukin-14∝ transgenic mice (IL-14∝TG), an animal model of Sjögren's disease. IL-14∝TG mice exhibit features of Sjögren's disease, including the development of lacrimal and salivary lymphocytic infiltrates, spontaneous production of anti-Ro/La, lymphomas, loss of salivary function, and dry eye symptoms.[15] They also studied autoantibody emergence in non-obese diabetic (NOD) mice, a separate Sjögren's disease animal model that experiences lacrimal and salivary injuries similar to IL-14∝TG.[16] They made several important observations. First, IL-14∝TG and NOD mice (but not control mice) produced autoantibodies against several novel proteins: salivary protein-1 (SP-1), parotid secretory protein (PSP), and carbonic anyhydrase 6 (CA-6).[16] Second, on average, antibodies directed against SP-1, PSP, and CA-6 developed earlier in the course of illness in these animals than antibodies against Ro and La. (Figure V-1)

Prior work by the same group of researchers characterized histopathophysiologic stages of Sjögren's disease in the same mouse model.[15] In those studies, autoantibody deposition in salivary glands and decreased salivary flow were present at 6 months; however, lymphocytic infiltration of the salivary and lacrimal glands had not yet begun. Lymphocytic infiltration could be demonstrated at 9 months in the submandibular glands, at 12 months in the lacrimal glands, and at 15 months in the parotid glands. By 18 months, malignant transformations were noted in submandibular and parotid glands, and salivary function had steadily declined.

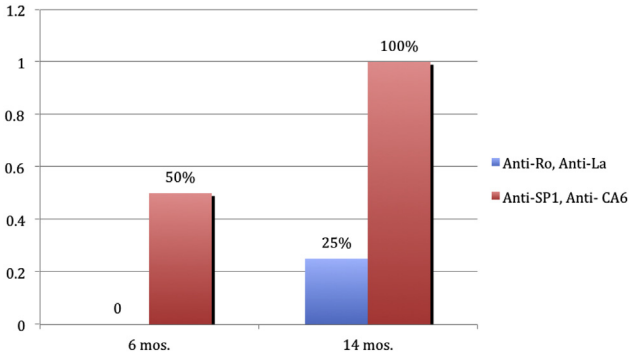

Figure V-1. Proportion of IL-14∝TG Mice with Autoantibodies at 6 and 14 Months. Source: Shen L, Suresh L, Lindemann M, et al. Novel autoantibodies in Sjogren's Syndrome. *Clinical Immunology*; 2012: 145; 251-5.

These findings suggest that, in mouse models, a humoral stage of Sjögren's disease, characterized by autoantibody production and deposition, precedes a cellular stage, characterized by progressive glandular inflammation, destruction, and malignant transformation.[15] Taken together, these findings indicate that, in mice, and potentially in humans, the appearance of novel autoantibodies coincides with earlier stages of disease—ie, prior to lymphocytic infiltration of glands.[15,16]

C. Diagnostic Importance of Novel Antibodies

Preliminary evidence suggests that these antibodies may be important in the human pathogenesis of Sjögren's disease as well. For example, these novel antibodies have been found in patients with Sjögren's disease both together and without anti-Ro and anti-La, as well as in patients with idiopathic dry mouth and DED.[16-19] As a diagnostic tool, antibodies to SP-1, PSP, and CA-6 may be useful for identifying early Sjögren's disease, particularly among patients who are anti-Ro/La negative.

In a cohort analysis of 20 patients who met the full diagnostic criteria for Sjögren's disease (including positive salivary biopsy) but who were anti-Ro and anti-La negative, 45% were positive for anti-SP-1 and 5% were positive for CA-6.[16,19] In a separate cohort of 29 patients considered to have early idiopathic xerostomia and xerophthalmia (symptoms for less than 2 years) who met at least three criteria for Sjögren's disease, 76% had anti-SP-1/ CA-6 antibodies present compared with only 31% with anti-Ro/La.[16]

While promising, additional larger studies are needed to understand the role of these autoantibodies in humans and their possible role in the pathophysiology of Sjögren's disease. For example, there is currently no known human homolog of SP-1, and the function of SP-1 is unknown.[16]

D. Novel Autoantibodies at a Glance

1. Specific Antibodies (Table V-1)

SP-1 is a salivary protein highly expressed in murine lacrimal and salivary glands. Its exact function is not known.

Table V-1. Novel autoantibodies and proteins they target

Protein	Site of Production	Proposed Function	Novel AutoAb associated with SS	Inciting event for AutoAb production
SP-1 (mouse; human equivalent has not been identified)[1]	Submandibular and lacrimal glands (murine)[1]	Unknown; May modulate T lymphocyte reactivity to salivary gland tissue[1]	Anti-SP1	Unknown; Possible cross-reaction to normal or abnormal flora in gut or lung[1]
PSP	Parotid and submandibular glands, gingival epithelial cells (human)[2]	Host defense[1,2,3]	Anti-PSP	Unknown; Possible cross-reaction to microorganism bound to cleaved PSP[1]
CA-6 [4]	Parotid and submandibular glands (human)[1,4]	Maintain saliva pH[4]	Anti-CA6	Unknown

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SP-1 = salivary protein 1; PSP = parotid secretory protein; CA-6 = carbonic anhydrase 6

Detection of antibodies against SP-1 is the most sensitive and specific indicator of early Sjögren's disease in the novel antibody group.[16]

PSP is produced and secreted by parotid and submandibular glands and is involved in binding and clearing infectious agents. Antibodies against PSP tend to occur concomitantly with antibodies against CA-6.[16]

Carbonic anhydrases are enzymes that regulate acid-base balance at various sites in the body including the kidneys. CA-6 is found in serous acinar cells of the salivary glands and is involved in the buffering capacity of saliva. Like anti-SP1, anti-CA-6 antibodies are hypothesized to appear early in the course of Sjögren's disease.[16] Pertovaara and coworkers found significantly higher levels of anti-CA-6 (and anti-CA I, II, and VII) in patients with primary Sjögren's disease compared to subjects with sicca symptoms but no Sjögren's disease.[20] The authors postulated that these antibodies may be involved in acid-base homeostasis in Sjögren's disease patients.

2. The Sjö™

The Sjö™ test is a panel of novel and classic biomarkers designed to help eyecare providers and/or rheumatologists assess Sjögren's disease autoantibody status among patients with sicca symptoms including dry eye. In addition to conventional biomarkers SSA, SSB, RF (IgM, IgG, and IgA), and ANA (titer and pattern), the Sjö™ test includes novel biomarkers anti-SP-1 (IgM, IgG, and IgA), anti-CA-6 (IgM, IgG, and IgA), and anti-PSP (IgM, IgG, and IgA). For each patient tested, resulting titers may be entered into an online interpretation app provided by the manufacturer, which suggests whether Sjögren's disease is likely or unlikely based on their complete autoantibody pattern as detected by the Sjö™ test.[21] Results may be printed but are not stored nor transmitted from the site.

3. Sjö™ Test Interpretation

As a new tool, best practices around Sjö™ testing have not been firmly established. Although preliminary evidence in mouse models and humans suggests that novel Sjögren's disease autoantibodies may be markers of early Sjögren's disease, these antibodies are not included in the current diagnostic criteria for Sjögren's disease. Additionally, the prevalence of these novel autoantibodies and closely related autoimmune disorders such as SLE and RA has not been studied in large groups of patients. In some instances, titers of novel antibodies may be consistent with those of conventional antibodies, lending additional support to either a positive or negative diagnosis. For example, a fully negative Sjö™ test panel (ie, undetectable titers for novel and conventional antibodies) supports a non-Sjögren's disease diagnosis and continued DED treatment with close follow-up. Similarly, a fully positive Sjö™ test (ie, elevated titers of novel and conventional antibodies) supports the diagnosis of Sjögren's disease and should prompt a referral to a rheumatologist and a dentist.

For patients with mixed results on Sjö™ testing—eg, positive novel antibodies but negative or borderline conventional antibodies—the meaning and implications are less clear. Take, for example, a patient who has a clinical phenotype consistent with Sjögren's disease but who does not fully meet the diagnostic criteria. If this patient tested positive for novel antibodies, some rheumatologists would diagnose the patient with Sjögren's disease and treat accordingly. Others

might choose to follow patients who are positive for novel antibodies more closely, suspecting that they are risk of developing Sjögren's disease over time. Still others might require continued workup, likely a lip biopsy, to establish a diagnosis and determine treatment. Further studies are needed to determine the optimal use of the Sjo™ Test in clinical practice.

4. Sjö™ Test Evaluation

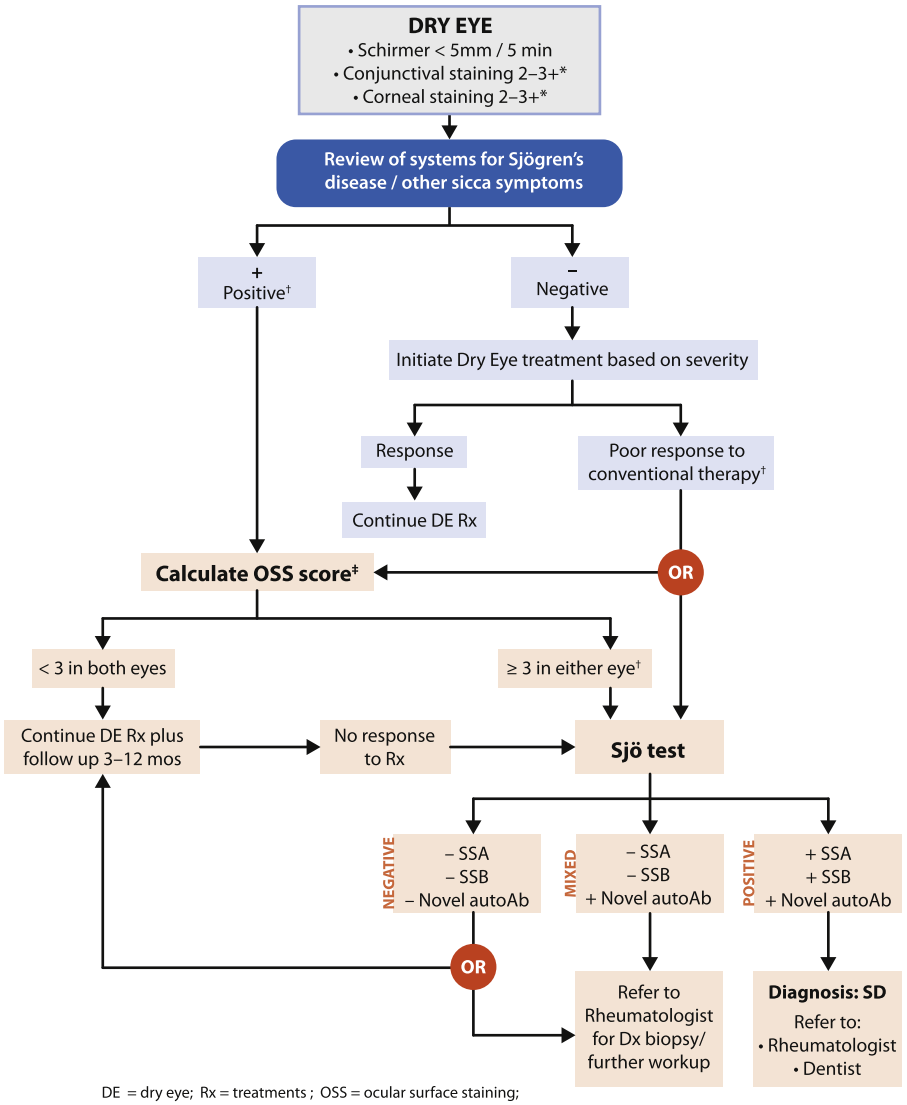
The chief advantage of detecting novel serum antibodies for Sjögren's disease is that it may allow earlier diagnosis of disease and thus enable earlier collaboration with members of the care team, including a dentist and rheumatologist. Earlier intervention could conceivably prevent the permanent loss of gland function and systemic complications.

Blood samples for Sjö™ testing are relatively easily obtained by simple finger prick using the lancet contained in the kit.[22] Most insurance covers the testing.

However, there are currently some limitations to use of the Sjö™ test. One difficulty with the Sjö™ test is that we lack evidence-based guidelines regarding which DED patients to test. Studies aimed at identifying DED patients who have the highest likelihood of having Sjögren's disease are needed. An algorithm for positioning the Sjö™ test within the diagnostic process is presented. (Figure V-2)

Data is also lacking on the meaning of a positive test for novel autoantibodies in a patient who does not meet other criteria for Sjögren's disease. Whether such patients will go on to develop the disease is currently unknown.

Finally, in some ophthalmic clinical settings, collecting and sending out blood specimens may present logistical



DE = dry eye; Rx = treatments ; OSS = ocular surface staining; mos = months; autoAb = auto antibody; Dx = diagnostic; SD = Sjögren's disease

*DEWS scoring
†Immediate referral to rheumatology may be appropriate at these points
‡SICCA scoring

Figure V-2. Algorithm for early diagnosis of Sjogren's disease.

challenges, including personnel, storage, patient flow, and reimbursement issues.

E. The Diagnostic Algorithm

Eyecare providers should maintain a high index of suspicion for Sjögren's disease among their patients with DED. The algorithm we present offers a rational roadmap for evaluating patients with significant DED. All patients with significant DED should undergo a detailed review of systems to uncover extraocular symptoms suggestive of Sjögren's disease. Patients with a positive review of systems for extraocular involvement consistent with Sjögren's disease or significant ocular surface staining and/or signs or symptoms refractory to standard DED treatment should be considered for referral to a rheumatologist for further workup. When in doubt, a rheumatology referral should be made sooner rather than later.

The Sjö™ test can provide eyecare practitioners a more robust profile of both novel and conventional autoantibodies associated with Sjögren's disease and ancillary support for (or against) a diagnosis of Sjögren's disease. As a complement to more preliminary assessments, the Sjö™ test serologies can assist eyecare providers with decision making around referral and management.[23] When used by a rheumatologist, the Sjö™ test may facilitate the diagnosis in patients with mixed or borderline findings suggestive of early Sjögren's disease.

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VI. SJÖGREN'S DISEASE MANAGEMENT

There is as yet no cure for Sjögren's disease, nor is there a remittive agent—ie, one that stops disease progression—as there are for other rheumatic conditions, such as RA. Until such agents are developed, the universal goals of treatment are to palliate symptoms, improve quality of life, and prevent complications. Rheumatologists have the additional goal of identifying patients who might benefit from immunosuppressive agents.

A. Patient Management Team

As a complex, chronic multisystem disorder, Sjögren's disease requires coordinated, cross-specialty care delivered by a team of medical experts. Ideally, the team will include a corneal specialist (or an ophthalmologist or optometrist with a special interest in DED), a dentist or oral medicine specialist, a rheumatologist, a primary care provider (eg, family practitioner or internist), and, depending on organ involvement, appropriate medical subspecialists (eg, pulmonologist for patients with lung involvement and a

gastroenterologist for gastrointestinal complications). At a bare minimum, the Sjögren's disease medical team should consist of an optometrist or ophthalmologist with significant training and experience in DED, a dentist, and a rheumatologist.

Patients should be offered educational and psychosocial support to cope with the significant physical and emotional toll of the disease. The Sjögren's Syndrome Foundation, Inc., Bethesda, M.D. (SSF) offers a range of invaluable resources for patients.[1] Additionally, professional counseling may benefit patients in order to detect, treat, and prevent depression and to optimize overall functioning and well-being.[2]

Generally, a rheumatologist (or sometimes a primary care physician) serves as the coordinator of care. Alternatively, when—as is often the case—the bulk of the symptoms are ocular, it may be desirable to have an ophthalmologist lead the care team. No matter who leads it, each member of the team should be well versed in and alert to the gamut of Sjögren's disease-related complications so that new complications can be identified as quickly as possible and prompt referrals made as needed.

B. Established Therapies

Established therapies used in the treatment of Sjögren's disease-related DED are essentially the same as those for the treatment of severe DED due to other causes. However, patients with Sjögren's disease are often more challenging to treat and are more likely to progress along the treatment algorithm due to lack of response. A paucity of clinical evidence exists to support the use of various modalities in Sjögren's disease treatment specifically, with no DED therapy achieving level I strength of evidence on recent review.[3] However, several small studies have been performed in Sjögren's disease patients (reviewed below) and provide some measure of evidence to the therapeutic knowledge base.

Consistent with the treatment of DED in general, agents/interventions used to treat Sjögren's disease are aimed at lubricating the ocular surface, reducing local inflammation, and/or increasing secretion or conservation of tears.[3]

C. Artificial Tears and Lubricants

Ocular lubricant drops—which contain a range of active and vehicular ingredients—are cornerstones of mild-moderate DED therapy. In clinical trials, improved signs and symptoms of DED have been associated with use of a wide variety of ocular tear preparations.[4] Active lubricating ingredients, inactive ingredients, and formulation can all influence the efficacy, the safety, and the patient experience with artificial tears. Solutions and suspensions drain quickly from the ocular surface and so require more frequent dosing than thicker formulations.

Topical ocular lubricants that come in a reusable bottle typically contain a preservative. Since preservatives can irritate the eye with frequent use, application more than four times per day should prompt the clinician to switch a patient to preservative-free unit-dose formulations, which can be applied more liberally. "Liquid gel" and "plus" formulations are more viscous and may provide longer lasting relief through prolonged contact of the lubricating ingredient against the ocular surface. Ointments containing petrolatum, mineral oil, or lanolin help retain moisture against the ocular surface and are best used at night due to their vision-blurring effect. Patients with allergy to wool may not tolerate lanolin-containing products.[5]

Patients who do not experience relief from a single topical lubricant may benefit from combining different artificial tears products for concomitant use.

Of the numerous topical ocular lubricants available over the counter, only a few active ingredients have been tested in clinical trials with Sjögren's disease patients. Hypotonic (150 mOsm/L) 0.4% sodium hyaluronate eye drops, 0.5% hydroxypropyl methylcellulose inserts, and sodium sucrose sulfate have been associated with improved symptoms and signs among Sjögren's disease patients.[3]

D. Ophthalmic Inserts

Soluble polymeric inserts (eg, hydroxypropyl cellulose ophthalmic inserts) are small rod-shaped pellets designed for placement in the inferior cul-de-sac of the eye to provide slow release of a lubricating agent throughout the day in place of repeated drops.[6] They are indicated for moderate to severe DED among patients who fail on artificial tear solutions or those with exposure keratitis, decreased corneal sensitivity, and recurrent corneal erosions. Care must be taken so as to not abrade the cornea on insertion. As with all artificial tear formulations, contraindications include hypersensitivity to any ingredient.

E. Autologous Serum Tears

Autologous serum tears are derived from patients' own blood, thus providing an unpreserved, non-antigenic, protein-rich tear substitute.[5] Because they contain growth factors, immunoglobulins, enzymes, vitamins, and other nutrients that support a healthy epithelial surface, they may offer greater benefit than over-the-counter artificial tears.[3] The process of making autologous serum tears requires testing and processing multiple tubes of blood by a compounding pharmacy; a 3- to 6-month supply of frozen serum aliquots is then returned to the patient. A single, multidose dropper is thawed and used daily.[7] Patients may find autologous serum tears soothing and longer lasting than artificial tears, possibly due to their biochemical similarity to natural tears.

Autologous serum tears have been shown to improve signs and symptoms of severe DED; they are also used to treat persistent epithelial defects, superior limbal keratoconjunctivitis, and other conditions.[4,7] They are generally safe and well tolerated; however, complications, including scleral vasculitis and immune complex deposition, have been reported. Problems with stability, standardization, and infection risk have not been entirely resolved. Contraindications may include infection with blood borne pathogens such as hepatitis C or HIV.[7] Autologous serum tears have not been well studied in Sjögren's disease; a few studies have

shown symptomatic improvement and reduced corneal staining associated with their use.[3]

F. Topical Ophthalmic Cyclosporine 0.05%

Studies suggest that treatment of ocular surface inflammation improves both symptoms and signs of ocular surface disease.[8]

Cyclosporine is an immunomodulatory agent formulated for topical ophthalmic use that is indicated for the treatment of keratoconjunctivitis sicca with an inflammatory component.[9] Treatment with topical cyclosporine has improved signs and symptoms of moderate-to-severe DED in clinical trials.[4,10] Adding topical cyclosporine to a patient's DED regimen can often help reduce the frequency of artificial tear dosing.

Topical ophthalmic cyclosporine 0.05% is contraindicated in patients with hypersensitivity to any of its ingredients. It is generally well tolerated; however, 15% to 20% of patients report stinging on application.[9] Stinging can be reduced by chilling drops in the refrigerator before applying them to the eye. Alternatively, patients may use a drop of artificial tear first as a barrier, wait for five minutes, then instill a drop of cyclosporine. Some clinicians prescribe a topical corticosteroid such as lotoprednol etabonate twice daily for the first two weeks of topical cyclosporine therapy to relieve the stinging and speed antiinflammatory effect.[11] A 3-year study of topical cyclosporine used twice daily demonstrated good tolerance and effect, but longer term topical cyclosporine use for the treatment of chronic DED has not been well studied.[2,12]

At least four studies have tested the effect of varying concentrations of topical cyclosporine among Sjögren's disease patients.[13-16] Objective improvements in TFBUT (one study), conjunctival staining scores (two studies), Schirmer test (one study), and conjunctival biopsy (reduced number of activated lymphocytes; one study) have been reported. One crossover study found no objective or subjective benefit of cyclosporine 2% over placebo. As a drug with a good safety record in DED and clinical and histopathologic evidence of efficacy, topical ophthalmic cyclosporine 0.05% is recommended for treatment of Sjögren's disease-related ocular surface inflammation.[3]

G. Topical Corticosteroids

Topical corticosteroids are potent inhibitors of ocular surface inflammation. In the treatment of DED, a number of ophthalmic corticosteroid preparations—loteprednol etabonate 0.5% ophthalmic suspension, fluorometholone, and methylprednisolone—have been associated with improvements in signs and symptoms, providing level 1 evidence for their short term use in steroid-responsive ocular conditions.[4,17]

The potential benefits of corticosteroids must always be balanced against the risk for ocular side effects, including raised intraocular pressure/glaucoma, cataract formation, and infection. Careful patient monitoring is critical to using them successfully in any condition. Due to the chronicity of Sjögren's disease, corticosteroids are somewhat less favored for topical antiinflammatory treatment in Sjögren's disease compared with cyclosporine; corticosteroids should be reserved for occasions when a pulse of fast, potent antiinflammatory action is required or for adjunctive use to relieve the initial stinging sensation of cyclosporine therapy.[11] Careful patient monitoring for adverse effects should accompany their use. A single study of short term (1 month) topical methylprednisolone therapy in patients with Sjögren's disease revealed early reduction in symptoms and corneal staining and improved Schirmer test, TFBUT, and goblet cell number by end of therapy. Long-term drug-free remission times were 56 weeks after one pulse therapy and 72 weeks after a second pulse.[3]

H. Dietary Modalities

In the past 100 years, industrialization of food production has resulted in major shifts in the typical Western diet and, consequently, physical health. Reduced availability of vitamins and other nutrients in soil and the foods it supports, increased consumption of saturated fats and processed items, and an inversion of the ratio of omega-6 and omega-3 fatty acid consumption have contributed to widespread obesity and undernourishment and contributed to various ailments that develop slowly over time.[18] Dietary modification and/or supplementation for the support of ocular health and the treatment of disease, principally the macula but also the tear film, are popular subjects of research.[18,19]

Long chain omega polyunsaturated fatty acids are vital to cellular health and are available only by dietary means. Omega-3 fatty acids, abundant in fish, flax seeds, and other sources, comprise a group of nutrients with an antiinflammatory role when consumed in adequate amounts. Diets chronically low in omega-3 fatty acids are thought to be proinflammatory and damaging to cells over time.[20] High dietary intake and/or supplementation with omega-3-fatty acids have been shown to curb inflammation in chronic autoimmune disease, including RA.[21]

There is evidence to suggest that oral fatty acid supplementation reduces symptoms and inflammation among patients with DED.[2,4,18] A prospective, masked trial comparing oral omega-3 supplementation (daily flax seed oil) with placebo (olive oil) revealed improvements in the systemic omega-6: omega-3-fatty acid ratio as well as improved TFBUT, OSDI score, and meibum quality.[22] While generally considered safe, potential benefit must be balanced with a possible increased risk for prostate cancer among male patients and bleeding problems in patients taking coumadin.[2] Among Sjögren's disease patients specifically, high quality trials have been few and results have been mixed.[3] Further research on the subject is needed.

I. Antiinflammatory Diet

Patients with an interest in dietary management should be counseled to follow an antiinflammatory diet, such as the diet recommended by the SSF.[23] Recommendations include increasing intake of colorful fruits and vegetables,

fiber, healthy fats, and spices with antiinflammatory properties such as tumeric, ginger, and garlic. Consumption of vegetable- or grass-fed, organic, free-range (rather than factory-farmed) meat is recommended. Avoidance of proinflammatory foods—including trans- or hydrogenated fats, refined oils, processed foods, and artificial sweeteners—is also recommended.

Adequate whole body hydration is also thought to support a healthy tear film.[18] Screening for and correction of vitamin deficiencies, particularly of vitamins A, B_{12}, and D, may benefit Sjögren's disease patients. Vitamin D is a pro-hormone with important immune regulatory capacity. Deficiency of vitamin D is common among patients with autoimmune diseases; levels have been shown to correlate with disease severity. Low vitamin D among Sjögren's disease patients may contribute to musculoskeletal pain, weakness, fatigue, and neuropathy and may increase risk for lymphoma.[24,25]

J. Punctal Occlusion

Artificial tears approximate but cannot replicate the biochemical complexity of the natural tear film, which is rich in biologically active molecules interacting with the ocular surface in ways that are only beginning to be elucidated. Blocking tear drainage via punctal occlusion retains the tears and prolongs the contact time between the tear film and the ocular surface and mitigates lacrimal gland underproduction aqueous deficient DED.

When preservative-free tear replacement and antiinflammatory therapies prove insufficient, punctal occlusion may be useful. Occlusion of the lacrimal canaliculi by plug insertion is the most common temporary method used in the treatment of moderate to severe aqueous deficient DED.[3] In clinical trials, punctal plugs have been shown to significantly reduce symptoms and signs of severe DED within 4 to 8 weeks of placement. Tear film quantity and quality are improved. Plugs are generally well tolerated; adverse events include epiphora, foreign body sensation, ocular irritation, and spontaneous plug ejection.[26] Some patients with inflammatory DED experience increased symptoms upon plug placement.[27]

Collagen plugs, which last four to seven days on average, may be tried on a temporary basis to test efficacy and tolerability prior to the placement of semi-permanent silicone plugs. Silicone plugs may be removed by an eyecare provider or may dislodge spontaneously.[26] Approximately 70% of tear volume drains through the inferior lacrimal canaliculus and 30% through the superior lacrimal canaliculus; placing punctal plugs in the inferior canaliculi alone may be sufficient to control symptoms.[4] After an adequate trial, plug placement in the superior canaliculus may be performed for added efficacy.

Patients with punctal plugs should be monitored regularly for their presence and position; they should also be cautioned against rubbing their eyes to minimize the risk of losing the plug. With repeated plug loss, permanent punctal occlusion by cautery or argon laser may be undertaken. Thermal cautery may be preferred as it is more effective and less expensive than laser cautery. In the most severe and recalcitrant cases, limited tarsorrhaphy (in which the eyelids are partially sewn together to narrow the palpebral fissure) may be considered.[2]

Several prospective studies have evaluated the use of punctal plugs in patients with Sjögren's disease. In one study, Sjögren's disease patients who underwent inferior punctum plug placement experienced significant improvement in Schirmer score and TFBUT at 1 year follow-up.[27] In a separate study, symptom and ocular surface staining improvement was associated with upper and lower puncta placement.[28]

K. Systemic Agents

Secretagogues are oral muscarinic receptor (cholinergic) agents that stimulate glandular flow of secretions. (In the same way that anticholinergics decrease moisture, secretagogues [cholinergics] increase moisture.) Two secretagogues, pilocarpine and cevimeline, have been shown in clinical trials to be effective in the treatment of oral and ocular sicca signs and symptoms, particularly at higher doses tested.[29-32] Pilocarpine is a naturally occurring plant alkaloid derived from the South American shrub *Pilocarpus jaborandi*.[29] Cevimeline is a quinuclidine derivative of acetylcholine.[32]

While approved in the US only for the treatment of xerostomia (related to radiation therapy or Sjögren's disease), secretagogues are sometimes employed in the treatment of extraoral symptoms, including DED that is recalcitrant to other treatments.[33,34] Pilocarpine and cevimeline are contraindicated in patients with uncontrolled asthma, hypersensitivity to ingredients, and/or intolerance of miosis (eg, acute iritis or narrow-angle glaucoma). These agents also carry cardiovascular, pulmonary, ocular, renal, and gastrointestinal warnings. Drug interactions include beta-adrenergic antagonists and drugs with parasympathomimetic and/or antimuscarinic effects.[2,34]

Common adverse effects include sweating, increased urinary frequency, and flushing.[24] It is important to note that the efficacy and side effect profile of the two agents vary within the class. Patients who fail one secretagogue may find success when switched to the other.[35] Excessive sweating and flushing are generally more common among patients taking pilocarpine than cevimeline. These effects may reduce tolerability, although increased sweating may be of benefit for patients with dry skin. Cevimeline is generally better tolerated; however, it is more likely to be associated with gastrointestinal side effects.[3,35] Cevimeline should generally be avoided in patients with Sjögren's disease-related intestinal involvement. Patients with constipation, on the other hand, may benefit from increased gastrointestinal secretions associated with cevimeline.

In prospective randomized, controlled studies, Sjögren's disease patients treated with oral pilocarpine reported reduced symptoms, including visual blurring and interference with focus and reduced reliance on artificial tears. Objective assessments revealed improved conjunctival

staining.[3] In one trial, sweating was reported as an adverse event among 40% of subjects.[29] In a separate series of randomized controlled trials evaluating cevimeline among Sjögren's disease patients, subjective and objective improvements were also noted.[3] Side effects, including abdominal pain, nausea, headache and sweating, were reported among 82% of subjects in one trial.[32]

L. Systemic Immunomodulators

Immunosuppressive agents are commonly employed in the treatment of systemic manifestations associated with Sjögren's disease. For example, hydroxychloroquine and methotrexate are used as first-line and second-line agents in the treatment of Sjögren's disease-related adenopathy and arthralgia; corticosteroids, azathioprine, or cyclophosphamide are standard treatments for interstitial pneumonitis; and rituximab has been shown to reduce Sjögren's disease-related fatigue. However, treatment of ocular manifestations of Sjögren's disease using systemic immunosuppression has proven largely ineffective. For example, trials of oral cyclosporine and systemic corticosteroid have shown no effect on Schirmer scores or Schirmer score and conjunctival staining.[3]

Hydroxychloroquine is a widely used immunomodulatory treatment for a range of autoimmune disorders; it is one of several disease modifying antirheumatic drugs (DMARDs) used in the treatment of RA.[36] In Sjögren's disease, hydroxychloroquine is the treatment of choice for fatigue, adenopathy, parotid swelling, arthralgias, myalgias, and hypergammaglobulinemic purpura.[37] Due to its regulatory effect on B-cells, hydroxychloroquine may play a role in lymphoma prevention, although this has not been substantiated.[3]

Studies evaluating the role of hydroxychloroquine on ocular manifestations of Sjögren's disease have been few. One showed a rebound increase in ocular signs and symptoms on withdrawal of hydroxychloroquine, indicating an ocular benefit for its use. A separate prospective trial showed no ocular benefit. Without better evidence supporting its use, hydroxychloroquine is not recommended for Sjögren's disease-associated sicca symptoms at this time.[3]

M. Other Methods

Moisture chamber goggles, hydrophilic bandage lenses, collagen corneal shields, and as a last resort, tarsorrhaphy may be considered in individual cases.[5]

Progression of ocular treatment for Sjögren's disease-related DED (a guideline based upon review of available research and collective clinical experience of this committee)

For mild Sjögren's disease-related DED:

- Discontinue medications with drying properties, eg, anticholinergic agents, if possible.[38]
- Start preserved artificial tears as needed up to four times daily.
- Address other sources of ocular irritation (eg, smoke exposure, prolonged computer use) or environmental dehydration (eg, air with low humidity).

For mild-moderate Sjögren's disease-related DED:

- Switch to preservative-free tears, for use up to every half hour as needed.
- Add ocular ointment or gel before bed for better nighttime relief. Ocular gels and ointments are available in four formulation types: preservative free; preserved; lanolin-free; and lanolin-containing. Lanolin is soothing to some patients and poorly tolerated by others.
- Consider long-acting hydroxypropyl cellulose pellets *or* higher viscosity artificial tear formulations (generally labeled "liquid gel" or "plus") for patients intolerant of or not responding to above.
- Add oral omega-3 fatty acid supplementation.

For moderate-severe Sjögren's disease-related DED with inflammatory component:

- Add topical antiinflammatory agent for persistent symptoms due to ocular surface inflammation.
  - Topical corticosteroid (eg, fluorometholone, loteprednol or prednisolone acetate, one drop each eye once daily for 1 month, then stop.)
  - Or, topical 0.05% cyclosporine drops (one drop in each eye twice daily). Studies suggest treatment of ocular surface inflammation may not only improve symptoms but ocular surface damage as well.[8]
- Consider autologous serum tears for patients intolerant of or not responding to above.

For Sjögren's disease-related DED with evaporative component:

- Treat for MGD/blepharitis as indicated:
  - Lid hygiene, scrubs, and warm compresses.
  - Topical cyclosporine 0.05% and oral omega-3-fatty acid supplementation for antiinflammatory action.
  - Topical antibiotic and lubricant, eg, erythromycin or azithromycin ophthalmic *or* oral tetracycline or doxycycline for antimicrobial/antiinflammatory actions.
  - Thermal pulsation technology may be used.[39]

For patients with severe Sjögren's disease-related DED who are using topical antiiflammatory agents:

- Punctal occlusion via plugs. Take a step-wise approach, testing effectiveness with temporary collagen plug then progressing to permanent silicone plug; start with lower canaliculi, then plug upper canaliculi as needed.
- Punctal occlusion via cautery or laser.
- Trial of oral secretagogues for patients in whom other therapies have failed.[29-32]
- Moisture chamber glasses or glasses with windshields.
- Therapeutic contact lens, such the PROSE device.[40,41]

N. New Biologic Agents (In Trials)

Biologic agents comprise a new, rapidly evolving category of advanced therapeutic molecules that target specific facets of immune dysregulation—such as cytokines, B-cell receptors, and co-stimulatory molecules—that contribute to oncologic and autoimmune disease. Their effectiveness stems from a genetically engineered design that typically

combines a highly specific antibody-binding domain to a functional or therapeutic domain that inhibits immune proliferation.[42] Due to good efficacy and overall safety, biologics are becoming increasingly important as adjuncts and second-line therapies in the management of RA, SLE, and other autoimmune diseases. However, cost (often exceeding $12,000 per year), risk for serious adverse events (including cytopenias, infections, and infusion reactions), and the need for intravenous administration limit their use.[42,43] Patients must be screened for occult infection, including tuberculosis, and brought up to date on vaccinations prior to initiation of biologic therapy; during and after treatment, patients must be carefully monitored.

While several biologic agents have been evaluated for the treatment of Sjögren's disease and show promise, none is currently recommended. Further research is needed to identify the best target molecule in Sjögren's disease and the most effective inhibitor of that target.

1. Anti-CD20 (B-cell)

Rituximab, the most thoroughly studied biologic in the treatment of Sjögren's disease to date, is a chimeric monoclonal antibody directed against the CD20 molecule on the surface of B-cells.[3] CD20 is expressed on normal and malignant B-cells and is essential to the regulation of B-cell proliferation. Rituximab is thought to work by depleting B cells through one or more of the following mechanisms: halting B-cell proliferation and/or inducing direct and indirect (complement-mediated and antibody-mediated) B-cell death.[44] Early depletion of the autoreactive B-cell population may allow for a resetting of immune tolerance.[45]

Rituximab is currently indicated in the treatment of RA, ANCA-associated vasculitis, and certain types of lymphoma and leukemia.[46] It is contraindicated during pregnancy and breastfeeding, active infection, live vaccination, and among patients with past medical history of hepatitis B, certain cancers, cardiovascular, or demyelinating diseases.[43] As a B-cell depleting therapy, rituximab is a logical choice for evaluation in Sjögren's disease patients, because B-cell dysregulation and proliferation are fundamental pathophysiologic features of the disease.

Several studies have demonstrated clinical improvement among primary Sjögren's disease patients with rituximab. In a randomized, placebo-controlled pilot study of rituximab in primary Sjögren's disease patients (N=17), Dass and coworkers demonstrated statistically significant fatigue reduction by visual analog scale (VAS) from baseline and improved social functioning score by Short Form 36 Health Survey (SF-36).[47] Other endpoints, including Schirmer test, salivary flow, and the primary endpoint of fatigue reduction vs. placebo, did not reach statistical significance. Five serious adverse events, including heart palpitations (1) and infusion reactions (2), were reported.[10]

In a separate randomized, placebo-controlled, double-blind trial (N=32), treatment of primary Sjögren's disease patients with rituximab resulted in significant improvement in stimulated and unstimulated salivary flow rates, lacrimal function as demonstrated by lissamine green staining, and VAS of oral and ocular dryness when compared to baseline. Schirmer test and TFBUT were not significantly affected by rituximab treatment. The side effects reported included mild serum sickness (1) and infection (12).[48]

In a recent, prospective, nonrandomized trial among early, active Sjögren's disease patients (N=41), Carubbi and coworkers demonstrated significantly reduced overall disease activity using the European League Against Rheumatism Sjögren's syndrome disease activity index (ESSDAI) with rituximab compared to DMARDs (hydroxychloroquine, methotrexate, and cyclosporine).[45] Salivary flow rate and Schirmer test improved significantly among rituximab-treated but not DMARD-treated patients. There were no significant adverse events and no study discontinuations. The authors suggested that rituximab efficacy may be increased when therapy is initiated within two years of Sjögren's disease symptom onset.

The largest (N=120) double−blind, placebo controlled trial to date for rituximab in Sjögren's failed to show any statistically significant benefit for primary endpoints: $\geq$ 30 mm improvement of at least two of four visual analogue scales for global disease activity, fatigue, pain and dryness at six months. However, modest benefit was observed for global disease activity, fatigue and dryness at some earlier time points.[49]

2. Anti-TNF

Overexpression of the proinflammatory cytokine tumor necrosis factor (TNF) by immune cells and target tissues is thought to factor significantly in the pathophysiology of autoimmune diseases, including Sjögren's disease. Three anti-TNF biologic agents—etanercept, adalimumab, and infliximab—are currently used in the management of autoimmune diseases and at least two of these have been evaluated in patients with Sjögren's disease.[44]

Infliximab showed promise in early, open-label pilot studies, even inducing remission for up to 1 year following 3 months of therapy in a minority of patients.[44] Subsequent studies, however, including a randomized, placebo-controlled, trial (N=103), failed to show improvement in Sjögren's disease patients.[44,50] Similarly, etanercept has not proven effective in Sjögren's disease patients.[44,51]

Adalimumab is indicated for treatment of RA, ankylosing spondylitis, psoriasis, Crohn's disease, and ulcerative colitis.[52] It has not been evaluated in clinical trials in Sjögren's disease patients. In a case of primary Sjögren's disease complicated by Crohn's disease, adalimumab therapy induced remission of both diseases (diarrhea and arthralgia by 2 months and complete symptomatic remission by 4 months), which was sustained for the duration of follow-up ($>$ 1.5 years).[53]

TNF-α inhibitors are sometime used off label to treat inflammatory joint and muscle pain in Sjögren's. However, further study is required to define the role of anti-TNF therapies in Sjögren's disease, and at present none are recommended.

3. Anti-CD80/86

T-cell activation, which is thought to play an important role in autoimmune inflammation, including Sjögren's disease, requires co-stimulation of CD80/CD86 and CD28 molecules.

Abatacept is a cytotoxic T-lymphocyte-associated-4 protein that blocks CD80/86, thus interrupting CD28-induced T-cell activation.[43,54] It is indicated for the treatment of adult and juvenile RA.[54] Abatacept has also been used off-label in the treatment of polyarthritis associated with SLE.[43]

A recent, open-label pilot study (N=15) demonstrated safety and some efficacy in the treatment of primary Sjögren's disease. Treatment was associated with improvements in the numbers of lymphocytic foci, disease activity, fatigue, and other patient-reported symptoms, laboratory parameters, and quality of life compared to baseline; however, salivary and lacrimal function were not improved.[55]

4. Anti-BLyS

B-cell activating factor or B-lymphocyte stimulator (BLyS) is thought to stimulate the differentiation of B-cells and protect B-cells from apoptosis. An anti-BLyS biologic, belimumab is a human monoclonal antibody designed to bind and inhibit the soluble form of BLyS, thus disrupting the survival of B-cells including autoreactive B-cells.[43,56] Belimumab is currently indicated for the treatment of mild to moderate SLE.[43]

In a recent, open-label phase II trial (N=30), patients with primary Sjögren's disease treated with belimumab experienced statistically significant improvements from baseline in disease activity, patient-reported symptoms, and dryness (by VAS); salivary flow and Schirmer test were unaffected.[57]

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VII. THE SJÖGREN'S SYNDROME FOUNDATION: A RESOURCE FOR DOCTORS AND PATIENTS

The SSF is the only national nonprofit organization that specifically serves Sjögren's disease patients and the health care professionals who diagnose and treat them. The SSF provides patients with practical information and coping strategies, advocates for Sjögren's disease patients in the US and abroad, and operates as the leading clearinghouse for medical information on Sjögren's disease. Founded in 1983, the mission of the SSF is to:

- Educate patients and their families about Sjögren's disease.
- Increase public and professional awareness of Sjögren's disease.
- Encourage research into new treatments and a cure.

A. Major SSF Initiatives

The SSF is currently engaged in numerous national and international initiatives that will help clinicians diagnose, manage and treat Sjögren's disease patients. Here are some initiatives that eyecare professionals should know about:

1. Shorter Time to Diagnosis

The SSF is committed to shortening the lag time between patient suffering and disease recognition. Ophthalmologists and optometrists are critical to this pursuit, as dry eye symptoms are the most frequent complaint of Sjögren's disease patients.

A major 2007 SSF study executed by Harris Interactive found that 92% to 94% of Sjögren's disease patients consider dry eye symptoms to be their most significant complaint. In addition, 97% to 98% of Sjögren's disease patients had used eye drops and/or ointments at one time, and 92% to 93% of them currently use those medications. For Sjögren's disease patients, eye drops and ointments were the most commonly used of all medications. Diagnosis took nearly 7 years from onset of symptoms.[1]

A smaller SSF study carried out by Polaris Marketing Research in 2012 looking at recently diagnosed Sjögren's disease patients again found dry eye symptoms to be their chief complaint. In this study, 69.9% of Sjögren's disease patients rated dry eye as their most difficult symptom. When asked which health care provider diagnosed them, the majority said a rheumatologist (50%), the second largest group cited their primary care physician (18%), and the next largest group said they were diagnosed by an ocular specialist (8%).[2]

Since 2007, the delay in diagnosis has improved slightly to an average of 4.7 years, a duration still considered much too long by the SSF.[2] Thus, the SSF set a "5-Year Breakthrough Goal" in 2012 "to shorten the time to diagnose Sjögren's by 50% in 5 years" and launched major initiatives to combat the delay. Interim polls are demonstrating that time-to-diagnosis is improving significantly, and the SSF hopes to reach its goal of an average of 2.5 years from onset of symptoms to diagnosis by 2017.

2. Better Diagnostics

Encouraging the development of novel diagnostics became a natural priority for the SSF to help reach its 5-Year Breakthrough Goal. New and better diagnostics should also encourage clinical trials in Sjögren's disease and help raise professional and public awareness of the condition. The SSF Research Grants Program has most recently emphasized research projects that could lead to better diagnostics, and the SSF is partnering with companies producing or investigating new diagnostics in Sjögren's disease. Examples of the latter include the new Sjö™ serum test, which identifies proteins that may appear earlier in the disease course than traditional markers. The SSF is also supporting work on salivary biomarkers that is currently undergoing validation.

3. Improved Clinical Trials

The SSF has launched an international clinical trials consortium to increase interest in developing new therapeutics for Sjögren's disease. As part of the consortium's efforts, the SSF has hosted ongoing discussions to ensure that the latest classification criteria and outcome measures are internationally validated and accepted. The SSF is also working with government agencies to establish guidance documents for clinical trials and identifying companies that focus on new therapeutics or have therapies already in existence for closely related diseases and symptoms. The consortium then links those companies to medical centers that have Sjögren's disease populations that meet their trial needs and experienced investigators to oversee those trials.

4. Dry Eye Initiatives

The SSF hopes to participate in the next International DEWS, sponsored by the Tear Film & Ocular Surface Society (TFOS), which is planning to update earlier findings. The 2007 DEWS led to groundbreaking reports on all aspects of DED, including classification and epidemiology; diagnosis, management and treatment; and research and clinical trial design. Made publicly available by TFOS and published by *The Ocular Surface*, the DEWS Report dramatically changed the clinical and research landscape for dry eye.[3,4]

Another TFOS special meeting held in 2010 on "Global Treatments for Dry Eye Syndrome: An Unmet Need" included an SSF patient speaker to provide "The Voice of a Patient" and ensure that attendees understood the human aspects of dealing with DED and Sjögren's disease, making their mission all that more crucial. This meeting, attended by SSF staff and medical members, addressed the challenges of getting new treatments to market.

5. Clinical Practice Guidelines

The SSF Clinical Practice Guidelines initiative is creating the first-ever guidelines for managing and treating all aspects of Sjögren's disease. The largest medical professional initiative undertaken by the SSF to date, the Guidelines process involves more than 100 hundred specialists who are engaged in a highly rigorous process to develop recommendations on every aspect of Sjögren's disease. Goals are to provide consistent, high quality care, guide insurance reimbursement, and highlight areas where research is needed. Final recommendations will be publicized in professional journals, at professional meetings, through SSF publications, and online.

6. Access to Social Security Disability

Finally, the SSF obtained a specific listing for Sjögren's disease under Social Security Disability in 2008. Previously, Sjögren's disease patients had to meet criteria for related diseases that often did not fit their condition and were spread throughout the disability guidelines. The new criteria have all disabling aspects of Sjögren's disease in one place, including the disabling aspects of DED, making the application and approval process much easier for patients and their physicians.

B. SSF Resources for Clinicians and Patients

Resources available from the SSF help clinicians and patients stay up-to-date with the latest information about Sjögren's disease diagnosis and treatment, making the jobs of those who care for patients with Sjögren's disease easier.For the clinician, the SSF offers:

- **Complimentary brochures for clinician's offices.** These include "What is Sjögren's Syndrome?" "Dry Eye: A Hallmark Symptom of Sjögren's Syndrome," and more subjects related to Sjögren's disease. Hard copy brochures can be mailed to a doctor's office and also may be downloaded from the SSF website at www.sjogrens.org.[5]
- **Complimentary resource sheets.** Available online at www.sjogrens.org and through the SSF professional newsletter, these include "Questions to Ask Your Doctor About Sjögren's Syndrome and Dry Eye" and one-page tip sheets on managing DED.
- **Complimentary subscription to the *Sjögren's Quarterly*.** This SSF publication for health care professionals includes "Clinician's Corner," a feature for clinicians on specific aspects of Sjögren's disease, clinical studies,

clinical and research news and abstracts of interest, reports on Sjögren's disease research, and information on SSF initiatives of interest to professionals.

- **Annual national patient conferences.** While these conferences are geared toward a patient audience, health care professionals also frequently find the talks by clinicians and researchers useful. Complimentary registration is provided for health care professionals, and audiotapes on topics of interest can be purchased from the SSF.
- ***The Sjögren's Book.*** Published by the SSF and Oxford University Press, this comprehensive and authoritative book offers chapters on every topic associated with Sjögren's disease. It's a must-have for patients and clinicians alike and can be ordered from the SSF website.
- **SSF Website** (www.sjogrens.org). A special section for health care professionals and researchers provides information on SSF resources and programs.[6]

For patients, the SSF offers:

- **Support groups.** The SSF has over 65 support groups in cities across the US and Canada as well as an additional 200 telephone contacts. The SSF also coordinates a website page for the International Sjögren's Network, which includes groups from around the world providing assistance and support to Sjögren's disease patients.
- ***The Moisture Seekers*** **newsletter.** Published 10 times a year, this newsletter contains practical tips and the latest information on Sjögren's disease for patients and is mailed to those who join the Foundation.
- **Annual national patient conferences.** Held in a different US city each year, this two-day conference draws more than 400 patients and family members to hear educational talks on different aspects of Sjögren's disease and provides a unique opportunity to interact with other patients and meet health care professional speakers. SSF members receive a discounted registration.
- **Patient education sheets.** As noted above, these can be obtained from health care providers who receive the *Sjögren's Quarterly* or downloaded from the SSF website.
- **Books and other resources.** These are available from the SSF on topics ranging from coping with the disease to understanding and managing symptoms and complications. Discounts are provided for SSF members.
- **Media sources for information and support.** The SSF offers education and involvement via its website, Facebook, and Twitter.
- **Advocacy, awareness and fundraising initiatives.** The SSF advocates for all stakeholders and offers opportunities to join in activities to increase awareness and raise funds for the SSF. For advocacy, for example, the SSF campaigns for increased research funding and serves on coalitions working to include medically necessary over-the-counter products and drugs such as moisturizing eye drops and ointments covered by flexible health spending accounts.

C. Looking Ahead, Together

Treating Sjögren's disease patients means treating a systemic disease with manifestations that must be addressed by different specialists. Forming partnerships—between doctors, between doctor and patient, and with the SSF—is essential. For ophthalmologists and optometrists, this means working closely with the patient's rheumatologist or primary care provider and maintaining awareness that ocular symptoms may reflect systemic disease. Referrals to other key specialists and regular communication with those specialists are important to ongoing treatment of Sjögren's disease patients.

A partnership between clinician and patient is also vital for good care. Asking patients the right questions initially can lead to a more rapid diagnosis; and regular communication throughout management is crucial to a patient's overall care. Patients should be empowered to play active roles in their own management, communicating openly about symptoms and taking charge of basic tasks such as humidifying the environment; using warm, wet compresses; and applying moisturizing drops before feeling dry.

The SSF is an essential partner for clinicians, patients, patients' families, companies and other stakeholders in Sjögren's disease. The Foundation works to catalyze new ideas, support research, and increase awareness and education in Sjögren's disease. Fortunately, the tools we have available for diagnosing, managing and treating Sjögren's disease, as well as the expanding knowledge base, are changing and improving. Joining the SSF and taking advantage of the many resources it has to offer will keep health care providers on the cutting edge of their profession. To learn more about the Foundation and sign up for brochures and the *Sjögren's Quarterly,* visit www.sjogrens.org.

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