A Review and Update of Sjögren's Syndrome: Manifestations, Diagnosis, and Treatment

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Abstract

Sjögren's syndrome is an autoimmune disorder that affects approximately 1% of the population. It is a disease that in recent years has not been studied extensively, but for which much study is needed. Diagnosis of this disease is extremely difficult. Until recently no strong consensus on diagnostic criteria has been published. The disease can cause dry eyes, dry mouth, vasculitis, and neurologic disease, and each symptom may be at times correctly attributed to Sjögren's or incorrectly attributed to another disease. Because it affects many different areas, many specialists (rheumatologists, primary care physicians, ophthalmologists, and dentists) have to be educated about Sjögren's syndrome's pathogenesis, manifestations, diagnosis, and treatments to manage this disease and help improve these patients' quality of life.

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Sjögren's syndrome (SS) is an autoimmune disorder affecting approximately 1% of the adult population. Like many autoimmune disorders, SS exhibits a striking gender bias resulting in a female predominance of approximately 9:1.[1]

It is a disorder of middle age, beginning most often between the ages of 30 and 60 years. Many investigators feel that SS is underrecognized and therefore underdiagnosed. There may be many reasons for this: 1) The early symptoms of dryness affecting the eyes and mouth may be confused with atopic disease and anxiety respectively; 2) Because this disorder primarily involves middle-aged women, symptoms of cutaneous, oral, and vaginal dryness may be thought to be associated with menopause; 3) Patients often present to multiple specialists, each of whom sees only a very restricted part of the syndrome; 4) There is lack of universally accepted classification criteria.

The cardinal manifestation of SS is dryness as a result of exocrine dysfunction. Ocular and oral dryness are extremely common symptoms, especially in an aging population. The term "sicca" (*Lat.* dry) is usually reserved for patients who have some dryness of their eyes and/or mouth but do not meet criteria for the diagnosis of SS. Primary SS is usually defined as dry eye and dry mouth accompanied by salivary swelling. Secondary SS is defined as dry eye or dry mouth in the presence of a major autoimmune connective tissue disease such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). Approximately 50% of SS patients have primary disease. Of patients with a major connective tissue disease, RA patients have the greatest prevalence of SS. Approximately 20% of RA patients have SS. Many patients with primary SS also exhibit a variety of organ-specific autoimmune conditions including thyroiditis and primary biliary cirrhosis (45% and 72%, respectively).[2,3] Thus, SS has a strong association with systemic and organ-specific autoimmunity.

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Pathogenesis of Dryness

Strand and Talal[4] have coined the term "autoimmune exocrinopathy" to describe the primary pathologic process of SS. As this term suggests, exocrine dysfunction in SS is not only confined to the lacrimal and salivary glands but is systemic in nature and can affect the function of exocrine glands in the female genital tract, skin, nose, trachea, and gastrointestinal tract. Microscopic examination of involved exocrine tissue reveals inflammatory changes marked by infiltration with lymphocytes, monocytes, and plasma cells. Infiltrating lymphocytes display a predominance of the CD4+ phenotype, which is enriched 3-fold compared with CD8+ T cells.[5] It has been assumed that eventual replacement of normal glandular tissue with inflammatory cells results in progressive exocrine gland dysfunction. Although this process most likely plays a role in pathogenesis, clinicians are commonly confronted with patients who are clinically very dry but whose minor salivary gland biopsies display modest inflammation. Conversely, patients whose exocrine tissue appears virtually replaced by inflammatory cells may only complain of mild dryness. The clinical scenario described above suggests that direct glandular replacement may not be the sole mechanism of glandular dysfunction. Recently, 2 other theories have gained importance in SS pathogenesis. Apoptosis of glandular cells, particularly ductal cells, has been demonstrated in SS. It is hypothesized that glandular dysfunction caused by apoptosis may precede inflammatory infiltration.[6] Initial apoptotic events may be caused by viral infection by a variety of salivary-tropic agents including Epstein-Barr virus (EBV) and hepatitis C virus (HCV). The development of a disorder highly similar to SS in human immunodeficiency virus (HIV)-infected patients is an example of a striking association between a viral infection and SS. Apoptosis of glandular cells may be the event that exposes nucleosomal and ribosomal particles to the immune system resulting in the typical autoantibody response (antinuclear antibody [ANA]; SS-A and SS-B) observed in SS. In addition to ANAs, the presence of organ-specific-type autoantibodies has recently been described in SS, specifically, antibodies to the M3 muscarinic receptor.[7] Such antibodies would cause glandular dysfunction in a manner similar to that caused by antithyroid stimulating hormone receptor antibodies in autoimmune thyroiditis. Autonomic dysfunction, as documented by altered blood pressure responses to valsalva, hand grip, and standing in 69% of patients in 1 series of primary SS patients,[8] may be more prevalent than realized in SS and may contribute to glandular dysfunction.

Table 1. Symptoms and Signs of Ocular Involvement in Sjögren's Syndrome

Symptoms
■ Foreign body sensation
■ Redness
■ Inability to tolerate contact lenses
■ Photophobia
■ Ocular fatigue
■ Eyelids encrusted in the AM
Signs
■ Diminished Schirmer strip readings
■ Corneal staining with vital dyes
■ Conjunctivitis
■ Mucous threads
■ Filamentary keratitis
■ Diminished tear breakup time

Ocular Manifestations

Although the most prominent ocular manifestation of SS is the dry eye, patients often are not aware of dryness as a presenting symptom (**Table 1**). Instead, patients may complain of a foreign body-type sensation as manifested by scratchiness, grittiness, or irritation from a "grain of sand." These symptoms may be interpreted by the patient and physician alike as atopic in nature and may prompt referral to an allergist. An early manifestation of the dry eye is the inability of the patient to tolerate contact lenses. Other common symptoms of dry eye include photophobia, redness, and ocular fatigue. Thick

mucous strands may cause blurring of vision and the eyelids may be encrusted, especially upon awakening. If the condition persists and is untreated, symptoms may reflect complications of dry eye including pain, intense photophobia, and discharge indicative of corneal abrasion, and possibly infection. Rarely, patients may present with an orbital mass, which represents a swollen lacrimal gland. It should be noted that symptoms of dry eye are nonspecific and ophthalmologic referral is appropriate. Examination may reveal a paucity of tears in the conjunctival sac. The conjuctivae may appear injected. Specific maneuvers are available, such as the Schirmer test, which will quantitate dryness, and the slit lamp examination, which will evaluate corneal disease and provide semiquantitative scoring.

Oral Manifestations

In contrast to dry eye, patients will often directly complain of a dry mouth (**Table 2**). Physicians caring for SS patients are accustomed to seeing SS patients carrying plastic water bottles. These patients require a constant supply of moisture to be comfortable. The dry mouth patient will describe a parched feeling in the mouth, often extending to the throat. Eating is often difficult without supplemental liquids. Talal has popularized the "cracker sign" where a patient is asked whether he or she can chew and swallow a saltine cracker without any exogenous liquid. The dry mouth patient will often respond with visible disgust or by demonstrating a choking sign by bringing his or her hand up to the neck. Patients also may describe a thickened saliva and may experience dysgeusia. Many of the more severe symptoms associated with dry mouth are secondary to complications of chronic dryness.

As a result of a reduction in salivary volume and the subsequent loss of the antibacterial properties of saliva in the dry mouth, tooth decay is accelerated. In fact, unexplained rampant dental caries may be the first sign of a dry mouth. Caries occurring in unusual places such as the incisal surfaces and at the gingival line are common in the dry mouth. Enamel at the junction of fillings and crowns is particularly susceptible to decay in the dry mouth. "Fillings falling out" may also be an early sign of the dry mouth. For the reasons stated above, the dry mouth is also extremely susceptible to the development of intraoral candidiasis. Patients report a burning mouth and tongue, and angular cheilitis. During the course of their illness, the majority of SS patients will experience swelling of the salivary glands. The parotids are most commonly appreciated; however, the sublingual and submandibular glands may also be affected. Swelling may be bilateral or unilateral and may fluctuate with time. Patients may experience "glandular flares" manifested by periods of increased swelling accompanied by pain and tenderness. Thickened, inspissated saliva places SS patients at increased risk for formation of calculi, which may be incidentally found on imaging studies. Infectious parotitis or abscess presents as erythematous, painful swelling of the gland often accompanied by fever, chills, and malaise. The presence of a dominant, hard mass should raise suspicion of lymphoma.

Examination of the oral cavity of the SS patient often reveals multiple caries in the distribution noted above. Patients with

Table 2. Symptoms and Signs of Oral Involvement in Sjögren's Syndrome

Symptoms
■ Parched mouth
■ Accelerated or unusual dental decay
■ Swollen salivary glands
■ Alteration in taste
■ Difficulty chewing and swallowing dry foods ("cracker sign")
■ Burning and cracking of lips and corners of mouth
Signs
■ Dry, parchment-like mucosa
■ Caries at incisal surface or gingival line
■ Premature loss of teeth
■ Loss of filiform papillae of tongue
■ Angular cheilitis
■ Reduction of infralingual salivary pooling
■ Parotid and/or submandibular enlargement

more advanced disease may be edentulous or have complete dentures. The mouth appears dry and the mucosa is thin and parchment-like and a tongue blade will adhere to the tongue and buccal surfaces in a "sticky" fashion. Centers specializing in SS or dry mouth will measure salivary flow rate quantitatively[9]; however, by asking the patient to open her mouth and place the tip of her tongue against her palate for 1 minute, the clinician may estimate flow rate by observing infralingual salivary pooling. Massaging the parotid will yield little or no saliva from Stenson's duct. In the dry mouth, candidiasis is not manifested by thrush. Rather, there is extensive erythema of the oral mucosa and loss of filiform papillae from the dorsal surface of the tongue. Small amounts of thin, whitish exudate may be found on the tongue and buccal mucosa. Bilateral angular cheilitis is often observed. Examination of the parotid glands often reveals some degree of swelling, often appreciated as a subtle "grainy" enlargement. In severe cases, "chipmunk-like faces" indicative of massive bilateral glandular involvement is seen.

Table 3. Systemic Manifestations Associated with Sjögren's Syndrome*

- Musculoskeletal
  - Arthralgias (53)
  - Myalgias (12)
- Cutaneous
  - Dry skin (66)
  - Hyperglobulinemic purpura (15)
  - Vasculitis (11)
- Pulmonary
  - Xerotrachea (66)
  - Pulmonary infiltrate (20)
- Gastrointestinal
  - Esophageal dysmotility (90)
  - Pancreatitis (5)
  - Hepatitis (38-72)
- Renal
  - Renal tubular acidosis (12)
  - Interstitial nephritis (12)
- Neurologic (11)
  - Peripheral neuropathy
  - Cranial neuropathy
  - Central nervous system disease
- Hematologic
  - Leukopenia (22)
  - Anemia (6)
- Lymphoma (5-10)

*Mean percentage shown in parentheses.
Source: References 1, 33.

Other Xeroses

Dry nose is common and may lead to inflammation with subsequent congestion, crusting, and epistaxis. Xerotrachea may result in a chronic dry cough. Dry skin may lead to pruritis and excoriation. Rarely, secondary infection may occur. Vaginal dryness may lead to pruritis, irritation, and dyspareunia.

Systemic Manifestations

Twenty percent of RA patients have secondary SS; however, even patients with primary SS may experience musculoskeletal symptoms including arthralgias, transient synovitis, and myalgias (**Table 3**). Joint erosion and persistent polyarticular synovitis is extremely rare. Similarly, persistent and significant elevation in creatine phosphokinase (CPK) is extremely uncommon.

The most common cutaneous manifestation of SS is dryness. Dryness often leads to pruritis, excoriation, and occasionally superinfection.

Skin rash in SS often involves the lower extremities and may exist as a spectrum ranging from hypergammaglobulinemic purpura to leukocytoclastic vasculitis. Hypergammaglobulinemic purpura is caused by high viscosity of blood leading to extrusion of red blood cells in dependent areas. The presence of palpable purpura suggests cutaneous leukocytoclastic vasculitis.

The most common pulmonary symptom of SS is cough. Cough is often a symptom of xerotrachea. Pulmonary parenchymal lymphocytic infiltration is relativity rare and may occur in conjunction with the development of pseudolymphoma or lymphoma.[10]

Glomerulonephritis is rare in primary SS. Renal disease is much more likely to be manifested as a distal renal tubular acidosis

syndrome as a result of tubulo-interstitial lymphocytic infiltration.[11] Clinically, the initial presentation is mild-to-moderate hypokalemia and hyperchloremic acidosis. Rarely, SS can present as hypokalemic paralysis; the only early clues being significant hyperglobulinemia on a chemistry panel.

In addition to xerostomia, the entire gastrointestinal tract may be affected by SS. Esophageal dysmotility is common and in 1 study 90% of patients were affected.[12,13] More significant dysphagia may signify the presence of esophageal webs. Endoscopic surveillance may be required for symptoms of epigastric discomfort, fullness, and early satiety, which could indicate the presence of atrophic gastritis or a mucosa-associated lymphoid tissue lymphoma. Mild hepatitis and pancreatitis are often identified on routine lab testing. Hepatitis requires differentiation from hepatitis C and organ-specific autoimmune hepatitis, the latter associated with specific antibodies such as antismooth muscle (F-actin) and antiliver-kidney microsomal antibodies (LKM-1). Elevation of amylase may be as a result of salivary disease. Salivary (S) amylase may be differentiated from pancreatic (P) amylase by electrophoretic mobility[14]; however, this type of analysis is often not routinely available. Rarely, pancreatitis associated with primary SS may lead to attacks of abdominal pain and/or symptoms of malabsorption. Abdominal and/or renal vasculitis, if suspected, should be determined by celiac axis arteriography.

Neurologic disease is perhaps the most common significant extraglandular manifestation of SS and can involve the cranial nerves, peripheral nerves, and rarely, the central nervous system. One of the most common forms of cranial neuropathy seen in SS is trigeminal neuralgia. Glove and stocking-type peripheral neuropathy is also common; more rarely an ascending (Guillain-Barré)-type neuropathy may be seen. Progressive neuropathy especially with motor involvement (eg, foot drop) may indicate the presence of necrotizing vasculitis especially in the context of palpable purpura or cutaneous ulceration and may be demonstrated by muscle and nerve biopsy. The incidence of central nervous system disease in SS is controversial[15]; however, most investigators believe that it is exceedingly rare. Patients who experience demyelination, seizures, dementia, focal findings, or psychosis should be reevaluated for the presence of SLE, multiple sclerosis, primary angiitis of the central nervous system, antiphospholipid syndrome, or other etiologies.

One of the major concerns of internists and rheumatologists caring for the SS patient is the potential for the development of lymphoma. It has been estimated that a primary SS patient has an approximate 40-fold enhanced risk of developing non-Hodgkin's lymphoma (NHL) compared with age-matched controls.[16] NHL is largely B-cell in origin and may involve extranodal sites, often the salivary glands themselves. Other extranodal areas include the gastrointestinal tract, the lung, and the thyroid gland. Waldenström's macroglobulinemia may be hearalded by the onset of the hyperviscosity syndrome accompanied by lower extremity purpura. The clinician should be aware of signs suggestive of lymphoproliferation including significant increase in the size of the salivary glands, especially when accompanied by dominant masses, lymphadenopathy, splenomegaly, and pulmonary infiltrates. Longitudinal monitoring of laboratory parameters is appropriate. Development of a monoclonal protein, new onset leukopenia and anemia, and a loss of previously present specific autoantibodies (ie, ANA, SS-A/B) have all been associated with the development of lymphoma.[17] More recently, a study of 261 Greek patients revealed that the presence of a low C4 and cryoglobulins conferred an approximately 6- to 8-fold odds ratio for the development of lymphoma.[18] On occasion, a patient presents with significant increases in glandular swelling, and/or lymphadenopathy that is suggestive of a lymphoma. Tissue biopsy, however, is inconclusive revealing atypical lymphoid architecture not diagnostic for lymphoma. This condition is referred to as "pseudolymphoma" and may represent an

intermediate step in lymphomagenesis in the SS patient. Table 3 summarizes the categories of systemic involvement in SS and their relative frequencies. It should be remembered that the potential for referral bias may exist and that patients evaluated by internists and rheumatologists may display higher percentages of the systemic manifestations described above.

Table 4. Workup of Sjögren's Syndrome

Ocular
- Schirmer test
- Slit lamp exam with vital dye (rose bengal, lissamine green)
- Tear breakup time

Oral
- Dental exam
- Estimate of salivary flow
- Salivary scintigram
- Minor salivary gland biopsy

Systemic
- Complete history and physical exam
- Complete blood count, ESR, LFTs, BUN/Cr, ANA, RF, SS-A/SS-B, Total IgG,M,A, SPEP, thyroid-stimulating hormone, U/A
- Chest X ray

Other (as indicated)
- Salivary gland sonogram/magnetic resonance imaging
- Lymph node or bone marrow biopsy
- Additional laboratory testing
  - Rheumatologic (dS-DNA, complement, Sm/RNP, ACE)
  - Organ-specific antibodies (thyroid, liver, neurological)
  - Viral (hepatitis B,C; EBV; human immunodeficiency virus)

ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; BUN = blood urea nitrogen; EBV = Epstein-Barr virus; Cr = creatinine; ds-DNA = double-stranded deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; IgG,M,A = immunoglobulin G, M, A; LFT = liver function tests; RF = rheumatoid factor; Sm/RNP = anti-Smith/ribonucleoprotein; SPEP = serum protein electrophoresis; SS-A/SS-B = Sjögren's syndrome A and B; U/A = urinalysis.

Diagnosis and Classification

The proper diagnosis of SS rests on recognition of the characteristic clinical findings described above, eliminating differential diagnostic possibilities, and differentiating primary from secondary SS. Many common conditions cause dryness, including aging, dehydration, and medication. The classes of medication most associated with dryness are: antihistamines and decongestants, antihypertensives and diuretics, muscle relaxants, and psychotropic drugs. Systemic diseases causing infiltration and inflammation of exocrine glands may mimic SS by causing glandular swelling and dryness. Viral infections including mumps and mononucleosis can mimic SS. Recently, an increasing number of patients with hepatitis C infection have been reported with a sicca syndrome and whose salivary glandular tissue demonstrates an atypical lymphocytic infiltrate.[19] HIV causes a syndrome known as diffuse infiltrative lymphocytosis syndrome (DILS). These patients display nearly an exact replica of SS symptoms including dry eyes, dry mouth, salivary swelling, and a propensity to develop lymphomas.[20] They are more commonly male, however, and lack specific SS-A and SS-B antibodies, although approximately 10% may exhibit ANA and rheumatoid factor (RF). In cases where it may be particularly difficult to distinguish SS from DILS, histochemical study of salivary gland biopsies reveals a CD4+/CD8+ ratio of ~ 0.66 in DILS in contrast to a ratio of > 3.0 in SS. Lymphocytic infiltration of salivary glands in graft-versus-host disease may mimic SS.[21] In these individuals, skin changes may also mimic scleroderma. Patients with sarcoidosis may present with lacrimal and salivary swelling, hypergammaglobulinemia, bone muscle and joint pain, and pulmonary infiltrates. In most cases, the characteristic features of sarcoidosis should pose little difficulty in diagnosis. Amyloid infiltration may also result in salivary gland and tongue swelling and dry mouth. Metabolic disorders including anorexia and bulimia may result in a nonspecific sialoadenitis. Finally, spontaneous

lymphoma may arise in a salivary gland and mimic features of SS.

The workup for SS should proceed in a fashion designed to document the key features of SS and eliminate the disorders noted above (**Table 4**). This may involve the coordination of multiple specialists because the eyes, oral cavity, and head and neck need to be examined along with performance of a general rheumatologic examination, including determination of viral and autoimmune serologies. Ophthalmologic exam should include a Schirmer test to assess dryness. Most ophthalmologists familiar with SS prefer an anesthtasized Schirmer I test to measure basal secretion. A slit lamp exam to examine the cornea is of extreme importance. This is usually preformed in conjunction with instillation of a vital dye. Rose bengal is best known; however, more recently lissamine green has been utilized. The demonstration of punctate keratopathy on slit lamp exam confirms a diagnosis of keratocunjunctivitis sicca (KCS). KCS is indicative of long-standing dry eye. The time required for the tear film to dissipate can be timed and measured as the tear breakup time (BUT). Tear BUT is utilized in some classification criteria for SS, however, it can also be seen in dry eye conditions as a result of mucous abnormalities.[22] Workup of the salivary component may include measurement of the salivary flow rate and the assessment of salivary gland function utilizing a technetium scintigram before and after citrus stimulation. The salivary scintigram displays the degree of homogeneity of isotopic uptake, which has been shown to correlate with salivary flow rate.[23] A fractional secretion of isotope may also be calculated. Sialography is used by some clinicians to examine destruction of the normal ductal aborization pattern in SS. It could also be useful in demonstrating obstruction by a stone or neoplasm. Performance of this test is, however, extremely uncomfortable for the SS patient and in the opinion of the author should rarely be used. Sonography and magnetic resonance imaging examination promise similar results in a noninvasive manner.

Minor salivary gland biopsy has been considered the "gold standard" for the diagnosis of SS. Newer criteria sets allow classification as SS in the absence of biopsy in certain cases; however, biopsy should be performed in cases where there is a possibility of malignancy or infiltrative systemic disease. A sample of the minor salivary glands of the mucosa of the lower lip is obtained via a small intraoral incision. To be consistent with SS, the biopsy must display a focus score >1.[24] A focus is an aggregate of 50 mononuclear cells per 4 mm^2. Scattered mononuclear cell infiltration as is often noted on pathology reports is insufficient for diagnostic purposes. External incisional biopsy of the parotid gland is avoided unless there is a localized mass and local malignancy is strongly suspected. Otherwise, a facial scar and possibly seventh nerve palsy may occur.

Serological workup should include measurement of RF and ANA. These are prevalent in SS and generally point to an autoimmune etiology. But they are not specific for SS and can be seen in a wide variety of autoimmune, inflammatory, and infectious diseases. The "Sjögren's antibodies"—SS-A and SS-B—are more specific for SS but are seen in 30% and 15%, respectively, of SLE patients as well.[25] Women of childbearing age who are positive for SS-A and SS-B are at risk of having an infant with neonatal lupus erythematosus (NLE). NLE is caused by transplacental delivery of SS-A or SS-B antibodies to the fetus where they bind to antigens expressed by the developing myocardial conducting system.[26] This can result in congenital heart block (CHB). Approximately 5% to 10% of infants born to women with SS-A or SS-B have CHB. Other features of NLE include rash, leukopenia, and hepatitis. All symptoms of NLE except for CHB resolve by the time the infant is 6 months of age as a result of dissipation of the passively acquired maternal antibody. Infants with CHB may require permanent cardiac pacing.

Baseline quantitative immunoglobulins and protein electrophoretic studies should be obtained so that future comparisons can be made should lymphoproliferation

be clinically suspected.[25] Complete blood counts, routine chemistries, urinalysis, and chest X ray should also be obtained on initial workup to exclude hematologic, hepatic, and pulmonary and renal disease. Serologies for EBV, HCV, and HIV should be obtained as clinically indicated.

As mentioned above, the lack of universally accepted classification criteria has hampered attempts to standardize a diagnostic approach for SS. Criteria sets have been developed in the United States, Europe, and Japan. Some criteria sets require a positive biopsy and/or SS-A/B antibodies. Others require only a history of dry eyes and mouth and a positive ANA. The former may be too restrictive and exclude bona fide cases that lack SS-A/B (30% to 40%) or in whom biopsy is not feasible. The latter may include patients who have conditions such as fibromyalgia. Recently, a European-American consensus committee approved a criteria set that exhibits approximately 95% sensitivity and specificity for SS (**Table 5**).[27,28] Adoption of these criteria should aid clinicians in the diagnosis of SS.

Table 5. European-American Consensus Group Modification of the European Community Criteria for Sjögren's Syndrome*

- Symptoms of dry eye
- Signs of dry eye (abnormal Schirmer test or rose bengal exam)
- Symptoms of dry mouth
- Tests of salivary glandular function (abnormal flow rate, scintigram or sialogram)
- Minor salivary gland biopsy (focus score > 1)
- Autoantibodies (SS-A or SS-B)

*Definite SS requires the presence of 4 criteria, one of which must be either positive biopsy or autoantibodies.
Source: References 27, 28.

Table 6. Approaches to the Treatment of Sjögren's Syndrome

Moisture replacement and preservation*
- Ocular
- Oral
- Punctal occlusion
- Moisture chamber glasses

Moisture stimulation
- Physical
- Pharmacologic
  - Pilocarpine
  - Cevimeline

Systemic therapy
- Anti-inflammatory agents (NSAIDs)
- Corticosteroids
- Immunomodulatory agents (hydroxychloroquine; cyclosporine)
- Cytotoxic agents (cyclophosphamide)

NSAIDs = nonsteroidal anti-inflammatory drugs.
*A thorough compilation of available moisture supplements is provided by Drs. Vivino and Orlin (see reference 34).

Treatment

Therapy of SS can be viewed as having 3 phases (**Table 6**). The first phase consists of external moisture replacement or capture. This approach can be applied to the oral cavity, the eyes, nose, skin, and genital tract. The next phase consists of stimulation of endogenous secretions and has been proven to be effective mainly for xerostomia. This approach is currently under investigation for other xeroses including the eyes and skin. Finally, patients with systemic manifestations such as pulmonary disease, vasculitis, and pseudolymphoma may require corticosteroids, cytotoxic agents, and intravenous gammaglobulin.

Ocular Disease. Therapy of xerostomia begins with moisture replacement. Patients should be encouraged to use tear substitutes often. If irritation occurs with frequent use, preservative-free tears should be used. Lubricating ointments and methylcellulose inserts are generally longer lived; however, they may cause significant blurring and are often reserved for nocturnal use. Existing tears may be retained in the eye by blocking their drainage or by inhibiting their evaporation. The former may be accomplished by occluding the puncta by inserting collagen or silicone plugs (temporary) or by electrocautery (permanent). The latter may be accomplished by wearing goggles or glasses with specially constructed side chambers. These devices are not well

accepted by patients but are valuable in certain environmental conditions (ie, wind). Inflammation of the meibomian glands (blepharitis) may complicate the dry eye and can be treated with warm compresses, a cleansing of the lids, and a topical antibiotic when needed.

Oral Disease. Surprisingly, replacement of saliva is not as successfully accomplished as tear supplementation. Artificial salivas are available; however, they are generally felt by patients to be short lived and unappetizing. Oralbalance® is longer lived but is a gel that must be applied intraorally. Most patients find it most suitable for nighttime application. Patients should be counseled with regard to general environmental measures designed to enhance moisture such as the use of a humidifier and avoidance of forced hot air heating systems and excessive air conditioning. Emphasis should be given to fastidious dental care including frequent exams and office and home fluoride application. Patients should be advised to avoid retaining sugar-containing foods in the mouth for long periods of time. SS patients often chew gum or candy for the gustatory stimulus for salivation; only sugar-free products should be used. Some of the more severe symptoms encountered by the dry mouth patient are secondary to intraoral candidiasis. Physicians, dentists, and patients should be advised to recognize the signs and symptoms of oral candidiasis. Treatment should be initiated with mycostatin. The oral suspension (100,000 U/5 mL, qid for 10 days) is commonly used, however, contains significant amounts of sucrose and could therefore be cariogenic. Mycostatin vaginal tablets dissolved orally offer an alternative. Cotrimazole lozenges (10-mg lozenge dissolved in the mouth 5 times per day for 14 days) also may be used. Oral candidiasis is recurrent and often requires retreatment.

Secretory Stimulation. Patients whose symptoms of dryness are not optimally controlled by moisture replacement should be considered for treatment with secretory stimulants (secretagogues). Secretagogues stimulate muscarinic receptors in salivary glands and other organs, leading to enhanced secretion.[29] Because there is a poor correlation between length of disease, biopsy findings, and response to these agents, a trial of secretagogue therapy should be offered. Secretagogues stimulate muscarinic activity in multiple organ systems, thus, caution should be used in patients with asthma, narrow-angle glaucoma, acute iritis, severe cardiovascular disease, biliary disease, nephrolithiasis, diarrhea, and ulcer disease. There are 2 approved agents available for use as secretagogues in SS: pilocarpine and cevimeline. Both agents have been shown in controlled clinical trials to significantly increase salivary flow rate in SS.[29,30] Preliminary data suggest that other xeroses may be improved as well.[31] Pilocarpine is administered as 5-mg tablets qid. Cevimeline is administered as 30-mg capsules tid. **Table 7** compares the properties of these agents.

Treatment of Systemic Disease

As noted earlier for glandular symptoms, a proper diagnosis is essential when considering therapy for the systemic manifestations of SS. This is especially true when considering systemic symptoms because delineation from RA, SLE, scleroderma, and other rheumatic disorders can be problematic. Exclusion of other sys-

Table 7. Comparison of Muscarinic Stimulants for Sjögren's Syndrome

	Pilocarpine	Cevimeline
Dose form	Tablet	Capsule
Dose strength	5 mg	30 mg
Half-life	~1 hr	~5 hr
Peak onset of reaction	1 hr	1.5-2.0 hr
Major muscarinic side effects (%)	Diaphoresis (40)	Diaphoresis (19)
	Nausea (10)	Nausea (14)
	Rhinitis (9)	Rhinitis (11)
	Diarrhea (9)	Diarrhea (10)

temic disorders that can affect exocrine glands such as sarcoidosis, amyloidosis, HIV, and lymphoma is also crucial.

Minor musculoskeletal symptoms usually respond to nonsteroidal anti-inflammatory drug therapy. Elderly patients or patients with peptic ulcer disease should be considered for cyclooxygenase-2 inhibitors. Because erosive disease is rare, therapy with disease-modifying antirheumatic agents is usually unnecessary; however, hydroxychloroquine (HCQ) at doses of 6 to 7 mg/kg/day has been used to treat fatigue, arthralgia, and myalgia in primary SS. HCQ has not been shown to improve dryness; however, HCQ administration does result in reduction of acute-phase proteins and elevated immunoglobulin levels in primary SS.[32] Rarely, short courses of low-dose corticosteroid (ie, prednisolone 5 to 10 mg/day) may be necessary for very painful or disabling joint symptoms.

To combat cutaneous dryness, patients should be instructed never to dry completely after bathing but rather to gently blot the skin dry, leaving a slight amount of moisture remaining to be followed by application of a moisturizer. There is some data suggesting that secretagogues (such as pilocarpine) when taken at doses of 20 to 30 mg/day ameliorate the symptoms of dry skin. In cases of hypergammaglobulinemic purpura, tight or constricting elastic clothing should be avoided. Intermittent use of a mild corticosteroid cream may be useful to control pruritis. Mild cases of cutaneous leukocytoclastic vasculitis may be treated expectantly as described above. Severe cases manifested by necrotic or ulcerating lesions require more aggressive therapy. Initial suppression may be achieved with moderate doses of corticosteroid (0.5 to 1 mg/kg/day of prednisolone). This should be tapered as rapidly as possible with continued immunosuppression maintained with HCQ, 6 to 7 mg/kg/day; methotrexate, 7.5 to 2.5 mg/kg/week; cyclosporine A, 2.5 to 5.0 mg/kg/day; azathioprine, 1 to 2 mg/kg/day; or cyclophosphamide, 50 to 150 mg/day, depending on severity.

Xerotrachea can be managed with humidification, secretagogues, and guaifenesin 1200 mg bid. Cough and dyspnea associated with lymphocytic infiltration may be treated with moderate-dose corticosteroid but may require low-dose oral cyclophosphamide (50 to 150 mg/day). Frank lymphoma where demonstrated by biopsy requires standard chemotherapeutic intervention.

Treatment of mild-to-moderate renal tubular acidosis consists of supplementation with potassium chloride and alkalinization with potassium citrate. For cases resistant to replacement therapy or demonstrating evidence of renal insufficiency consideration of corticosteroid therapy (0.5 to 1.0 mg/kg) should be given.

Manifestations of gastrointestinal extraesophageal reflux disease are usually managed with antacids, histamine-2 blockers, and proton pump inhibitors. Intermittent endoscopic evaluation and intervention may be required. Sjögren's-associated hepatitis is often mild and may not require specific therapy. Persistent and progressive liver function test elevation may require therapy with prednisone and azathioprine. Standard measures for the management of acute pancreatitis or pancreatic enzyme deficiency should be employed. Corticosteroid therapy has not been proven to be useful and may itself be associated with pancreatitis and should be avoided unless abdominal vasculitis is suspected.

Cranial and peripheral neuropathy may be treated with low-dose tricyclic antidepressants or anticonvulsants, such as gabapentin 300 to 1800 mg/day. Symptomatic cases resistant to the above therapies may be treated with intravenous gammaglobulin 0.4 g/kg/day 5 times a day. When demonstrated by muscle and nerve biopsy, vasculitis should be treated with moderate-dose corticosteroid (~1 mg/kg/day with subsequent tapering) and cyclophosphamide (50 to 150 mg po daily). If felt to be as a result of primary SS, central nervous system manifestations should be treated aggressively with high-dose oral (1 to 2 mg/kg) or pulse intravenous (1g/day for 3 days) corticosteroid and daily (50 to 150

mg/day) or monthly intravenous pulse (0.5 to 1 g/m^2) cyclophosphamide.

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