Oral manifestations of Sjögren's syndrome

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Sjögren's syndrome is a chronic autoimmune disease complex characterized by inflammation of the exocrine glands, primarily resulting in keratoconjunctivitis sicca, hyposalivation and xerostomia, or dry mouth. Dry mouth is one of the most easily recognized components and may lead the clinician to diagnosis. Hyposalivation is more than an inconvenience, having a significant adverse effect on health and quality of life. Early recognition of this condition may minimize some of the adverse sequelae. A dental evaluation in patients with confirmed or suspected Sjögren's is recommended. The focus of this review article is to highlight oral manifestations of Sjögren's syndrome to include pathogenesis, clinical presentation, implications for health, diagnostic tools, management strategies and future perspectives.

Learning objectives

Upon completion of this activity, participants should be able to:

- List the clinical features of Sjögren's syndrome (SS)
- Describe the prevalence of extraglandular manifestations of SS
- Identify other conditions associated with SS
- Describe the diagnostic criteria of the European–American Consensus Group for SS
- Identify infections of concern in patients with SS

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Sjögren's syndrome (SS) is a common, progressive autoimmune rheumatic disease characterized by subjective dry mouth (xerostomia), dry eyes (keratoconjunctivitis sicca) and extreme fatigue. B- and T-cell lymphocytic infiltration of the exocrine glands leads to diminished salivary and lacrimal and gland function. Symptoms may be limited to a local effect on the salivary and lacrimal glands, or extend to include widespread involvement of multiple organ systems [1,2]. SS may impact the peripheral and central nervous system, muscles, bone marrow, joints, kidneys, pancreas, thyroid and other glands. Research indicates that systemic extraglandular manifestations, including lymphoma, may appear in 40% of individuals with primary SS and present in two ways: the development of lymphoepithelial lesions in several extra-exocrine gland tissues (i.e., bronchi, renal tubules or biliary ducts); and vasculitis related to the deposition of immune complexes due to B-cell hyperreactivity [3].

The disorder may occur alone (primary SS), or in combination with another rheumatic disease, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma or primary biliary cirrhosis, in which case it is classified as secondary SS. The disease affects women more frequently than men, with a reported female:male ratio of 9:1 [4]. A recent report from a Hungarian cohort indicated a higher involvement in men than previously reported, with a female:male ratio of 7:1 [5]. Although it has been described in children and adolescents [6,7], the onset of symptoms occurs most often during middle age [8]. Currently, the etiology of SS is not clearly understood, but appears to be multifactorial. It has been suggested that environmental agents may trigger SS in genetically predisposed individuals. Potential mechanisms underlying SS include disturbances in apoptosis [9–12], circulating autoantibodies against the ribonucleoproteins Ro and La [13,14] or cholinergic muscarinic receptors [15–17] in salivary and lacrimal glands, or cytokines [18]. These processes interfere with normal glandular function, and as the mucosal surfaces become sites of chronic inflammation, the disease appears to enter a self-perpetuating inflammatory cycle.

Depending on the classification criteria applied, estimates of its prevalence in the adult population range from 0.5 to 3% [19], making it one of the most common autoimmune disorders. However, due to the vague and diverse presentation of initial symptoms, the diagnosis is difficult and often takes several years. It is of utmost importance for all clinicians to be vigilant regarding the oral manifestations of SS, as the disease often manifests with initial complaints of 'dry mouth' and related oral complaints. The concerns of oral dryness, increase in dental restorations and crowns, oral ulcers and lack of taste and appetite, may be attributed to etiologies such as stress, dehydration, inadequate oral hygiene and medications, without a consideration of SS. The astute physician can provide proper patient education and necessary referral consultations to minimize the debilitating consequences of untreated oral complications of SS.

Diagnostic criteria

Several diagnostic protocols have been developed and revised as more is learned. To date, the American–European Consensus Group (AECG) 2002 classification criteria appear to be most universally accepted (Box 1) [20]. The AECG criteria require the presence of four of six criteria, which include objective criteria, oral and ocular symptoms, and either positive serum autoantibodies Ro/SS-A and/or La/SS-B or positive histopathology from a labial salivary gland biopsy.

Oral symptoms

As indicated in Box 1, oral symptoms include xerostomia for greater than 3 months and frequent water intake. To assist assessment of subjective dry mouth, positive responses to the following questions are very useful: the need to drink water to swallow foods, the need to keep a glass of water by the bed or frequent awakening at night due to oral dryness, the amount of saliva in the mouth feels inadequate, and difficulty speaking [21,22].

Saliva is secreted from three major paired glands (parotid, submandibular and sublingual) and from hundreds of minor salivary glands located throughout the submucosa of the oral cavity, with the exception of the anterior hard palate and gingiva. Stimulated saliva, produced during eating, is controlled by the autonomic nervous system. It aids chewing of food, formation and swallowing of a food bolus and digestion via the enzymes amylase and lipase. The parotid gland, which provides thin watery secretions, contributes significantly to stimulated saliva. Saliva secreted in the absence of apparent sensory stimuli related to eating is referred to as resting or unstimulated saliva. The parotid gland contributes 25% to unstimulated flow. The submandibular gland, a mixed mucous and serous gland, contributes 60%, and the sublingual and minor mucous glands each contribute 7–8% of whole saliva [23–25].

A continuous production of small amounts of saliva occurs throughout the day, often from the minor salivary glands in response to dryness of the oral mucosa and stimulation from movements of the jaw and tongue. This fluid covers the oral and pharyngeal cavities and is responsible for maintaining the integrity of the mucosa. As little time is spent eating during a 24-h period, resting saliva is a significant contributor to total salivary output. A lack of unstimulated saliva is a key factor in the sensation of dry mouth [26].

Easily recognized clinical indications of a diminished salivary output could include dry and/or chapped lips, salivary gland enlargement, lipstick on the anterior teeth, a lack of pooling in the floor of the mouth, thick or frothy saliva and examination gloves sticking to the tongue or buccal mucosa. Upon closer examination, the clinician might also observe signs of candidiasis. Multiple restorations, crowns and often decay at the cervical portion of the tooth, either just above the gingiva or on the root surfaces, can be observed (Figure 1). The tongue might appear fissured, slightly erythematous and/or depapillated, as shown in Figure 2. This clinical presentation is similar to the dorsal tongue appearance in a patient with vitamin B12 deficiency, which should be ruled out. Box 2 contains a list of clinical signs and symptoms of SS.

Objective salivary gland involvement
Sialometry

In SS, both quantitative and qualitative changes in saliva often develop early in the disease. The normal unstimulated whole salivary flow rate ranges from 0.3 to 0.4 ml/min, but the range is wide [27,28]. According to the AECG criteria for SS, severe hyposalivation is an unstimulated salivary flow rate of less than 0.1 ml/min. This represents an approximate reduction of 50–70% below normal.

To accurately measure the whole unstimulated salivary flow rate, it should be collected under standard conditions and calculated gravimetrically. Patients should refrain from oral hygiene procedures, smoking, eating and drinking for at least 2 h prior to the test session. Seated comfortably in an upright position, patients are instructed to allow their saliva to flow (drool) into a preweighed vessel for a period of 15 min. Sealed containers are then reweighed to determine the weight of saliva expectorated. The unstimulated salivary flow rate is determined by gravitation, using a scale with an accuracy to 0.01 g. Presuming

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Box 1. European–American Consensus Group Criteria for Sjögren's syndrome.

I. Ocular symptoms (positive response to at least one of three)
- Daily, persistent, troublesome eyes for more than 3 months
- Recurrent sensation of sand or gravel in the eyes
- Use of tear substitutes more than three times per day

II. Oral symptoms (positive response to at least one of three)
- Daily feeling of dry mouth for more than 3 months
- Recurrently or persistently swollen salivary glands as an adult
- Frequent drinking of liquids to aid in swallowing food

III. Ocular signs (positive result for at least one of two tests)
- Schirmer's test, performed without anesthesia (≤5 mm in 5 min)
- Rose Bengal score or other ocular dye score (≤4 according to van Bijsterveld's scoring system)

IV. Histopathology in minor salivary gland biopsy
- Focal lymphocytic sialoadenitis, with focus score ≥1 (a focus is defined as ≥50 lymphocytes per 4 mm^2 of glandular tissue adjacent to normal appearing mucous acini)

V. Salivary gland involvement (positive result for at least one of three)
- Unstimulated whole salivary flow (≤1.5 ml/15 min)
- Parotid sialography showing the presence of diffuse sialectasis (punctuate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
- Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies
- Presence in the serum of antibodies to Ro(SS-A) or La(SS-B) antigens, or both

Classification criteria
- Primary Sjögren's syndrome
  – The presence of any four of the six items, as long as either item IV (histopathology) or item VI (serology) is positive
  – The presence of any three of the four objective criteria (Items III, IV, V and VI)
- Secondary Sjögren's syndrome
  – In the presence of another connective tissue disease, the presence of item I or item II, plus any two from items III, IV and V
- Exclusion criteria
  – Past head and neck radiation treatment
  – Hepatitis C infection
  – AIDS
  – Pre-existing lymphoma
  – Sarcoidosis
  – Use of anticholinergic drugs (since a time shorter than fourfold the half-life of the drug)

Adapted from [20].

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that 1 g of saliva is equivalent to 1 ml, the measured volume is expressed as flow rate in ml per min [29,30]. While gravimetric analysis for whole unstimulated salivary flow rate might be cumbersome and too time-consuming for a busy practice, asking the patient to expectorate or 'drool' into a calibrated tube or cup for 10 min, as opposed to 15 min without stimulation, could be helpful. If the patient failed to produce enough saliva to meet the 1.0 ml designation on the container in 10 min, further assessment for hyposalivation would be indicated.

Figure 1. Tongue and dentition of primary Sjögren's patient. This photograph shows fissuring of tongue, advanced decay on the root surface (white arrow), recession and early root decay (blue arrow), five crowns (black arrow), and an edentulous space in the mandibular anterior, indicative of tooth loss.

Additional salivary gland collection techniques are available for measuring specific glandular secretions. Modified Lashley cups (Carlson–Crittenden cups) may be applied over Stenson's duct for collection of pure parotid gland saliva. For obtaining saliva from the submandibular and sublingual glands, syringe aspiration from Wharton's duct and Rivinus's ducts may be accomplished as well. Separate aspiration is challenging in clinical practice due to the close anatomical location of the sub-

Figure 2. Dorsal tongue in primary Sjögren's syndrome patient showing central depapillation, dryness and erythema.

mandibular and sublingual gland orifices and the common presence of communicating ducts between the submandibular and sublingual main ducts [31,32].

Imaging

In addition to unstimulated whole sialometry, objective evidence of salivary gland involvement may also be obtained using imaging techniques. A salivary scintigraphy using radioactive technecium-99m pertechnetate (Tc99) will assess gland function and show delayed uptake, reduced concentration and/or delayed excretion of tracer. A parotid sialogram may be performed using water-based radiocontrast dye injected into the Stenson's duct. Using conventional radiography, sialographic findings may reveal punctuate sialectasia and glandular atrophy. Abnormal filling defects diffusely distributed throughout glands may be seen. Due to the possibility of infection and blockage in the ducts, conventional sialography is used less frequently in contemporary practice. Modern imaging modalities, such as magnetic resonance sialography, allows visualization of the salivary duct system to the tertiary branches, and can be a useful, noninvasive method for assessment of complaints of dry mouth [33,34]. Renewed attention is being given to the use of ultrasonography for diagnostic purposes in patients with primary SS. It provides a noninvasive method to assess structural changes to salivary glands during inflammation [35]. A recent report found the detection of reduced volumes of both submandibular glands in patients with primary and secondary SS had a specificity of 93% and a sensitivity of 48% at the cut-off point of 3.0 ml. Of note, the volume of the parotid glands did not differ between the groups of patients [36].

Labial salivary gland biopsy

The labial salivary gland biopsy is performed on normal-appearing mucosa of the lower lip between the midline and commissure. Five or more accessory salivary gland lobules are examined histopathologically for the presence of focal chronic inflammatory aggregates. A cluster of 50 or more lymphocytes with some plasma cells is called a focus. The numbers of foci in a 4 mm^2 tissue section constitute the focus score. A characteristic histopathologic feature in minor salivary glands in SS is focal lymphocytic sialadenitis, as depicted in FIGURE 3. The foci are found adjacent to normal-appearing acini throughout the glands, and are often periductal [37,38]. For the current AECG criteria, a finding of one or

more foci within a 4 mm^2 area of glandular tissue is supportive of the SS diagnosis. Complete destruction of glandular acini, extensive fibrosis and dilated ducts would be more consistent with chronic sclerosing sialadenitis, not supportive of a SS diagnosis (Figure 4).

Currently, the labial salivary gland biopsy is considered the most reliable oral diagnostic test for confirmation of SS. However, clinicians are becoming increasingly aware that the labial salivary gland biopsy is not completely reliable, due to the potential for false-positive and false-negative results. In the past few years, the accuracy of the biopsy interpretation, impact on disease classification and diagnostic benefits of this procedure have been reviewed with mixed findings [39–42]. It is recognized that lymphocytic foci may be seen in non-SS patients, normal patients and as part of the aging process [43–46]. In addition, false-negative biopsies may be reported if inadequate tissue is obtained, or a sampling error occurs based on location.

Conversely, several studies report that significant focal infiltrates will not be present unless a connective tissue disease is present [47–49]. Previous studies examining the relationships among clinical, laboratory and histopathological findings in SS patients have shown varying results. While a number of investigators have reported significant correlations between biopsy findings and serological or salivary measures [50–52], others have found no relationship between these variables [53,54]. Some studies indicate that the lymphocytic infiltration in minor salivary glands, measured as a focus score, will increase over time [55]. In addition, it has been reported that, in SS patients, the highest focus scores belong to those with lowest whole unstimulated salivary flow rate [56]. It is interesting to note that focus scores are reported to be lower in SS patients who are cigarette smokers [57].

Autoantibodies

One of the main diagnostic tools for SS is the presence of circulatory autoantibodies to 60 kDa Ro/SS-A and La/SS-B. Antibodies occur in approximately 60–70% of patients with SS. Studies have suggested that levels of anti-60-kDa Ro and anti-La are correlated with earlier onset, longer disease duration, recurrent parotid gland enlargement and more intense lymphocytic infiltration of the minor salivary glands and extraglandular manifestations [4,58].

Recent studies have assessed correlations between salivary production and autoantibody profile. The anti-La titer was significantly

Box 2. Clinical signs & symptoms of Sjögren's syndrome.
Xerostomia, usually with hyposalivation
▪ Dysgeusia
▪ Dysphagia
Dry, chapped lips
Salivary gland enlargement
▪ Unilateral or bilateral
▪ Sometimes chronic once present
Tongue
▪ Fissured, erythematous
▪ Depapillated
High rate of dental decay
▪ Caries at cervical 1/3 of tooth and/or incisal edges
▪ Heavily restored dentition with restorations and/or crowns
Halitosis
Candidiasis
▪ Erythematous candidiasis
– Commonly on dorsal tongue, hard palate, inner aspect of lips
– Often under ill-fitting or poorly cleaned denture
▪ Pseudomembranous candidiasis
– Any intraoral site
– Commonly on buccal mucosa, soft palate and tongue

associated with salivary production rate, after age correction. Salivary production was greater in the group with anti-Ro alone than in the group with both positive anti-Ro and anti-La titers [59].

Impact of hyposalivation on health & quality of life

Significant salivary components

Protection against bacterial, viral and microbial agents is provided by enzymes and antimicrobial fluids. Enzymes such as lysozyme and peroxidase have antimicrobial and antiviral properties. Histidine-rich proteins, histatins, have strong anticandidal effects. Proline-rich proteins, which comprise a significant component of parotid saliva, have roles in lubrication and development of pellicle on the surface of teeth, which acts to reduce frictional wear. Immunoglobulins help protect the integrity of the oral mucosa as well.

Salivary electrolytes provide critical buffering and remineralization activities. Calcium, phosphate, bicarbonate and fluoride are of particular importance for oral health. The critical pH for saliva is 5.5–6.5. Below that pH, tooth enamel may demineralize. This process is inversely related to the concentrations of calcium and phosphate in the saliva [60]. Saliva is supersaturated with respect to hydroxyapatite, the main mineral of teeth. Thus, tooth enamel bathed with normal saliva is resistant
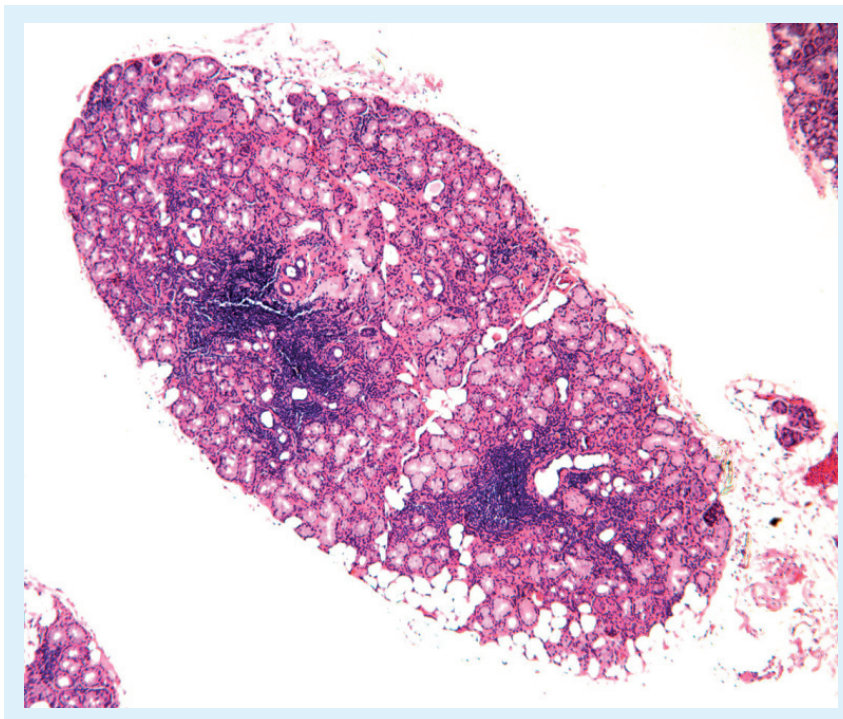
Figure 3. Labial salivary gland biopsy showing multifocal lymphocytic infiltration, consistent with Sjögren's syndrome. Magnification: 5×.

to dissolution. However, when saliva is acidified, dissolution proceeds. It is recognized that lightly softened enamel may experience remineralization, particularly in the presence of fluoride [61]. This underscores the need for fluoride intervention in SS patients with low unstimulated flow rate.

Mucins are glycoproteins that provide mechanical protection to tissues, prevent dehydration and facilitate lubrication of food. The mucous glycoproteins of saliva, such as MUC5B, MUC7 and proline-rich glycoproteins, play a major role in lubrication. This lubrication reduces trauma to soft tissues during mastication, swallowing and speaking. Primary SS patients with hyposalivation display a decrease in the concentration of mucin, MUC5B and amylase [62]. These glycoproteins also help maintain an intact layer of saliva (the salivary film) in contact with the oral mucosa, which prevents it from drying out. Salivary film thickness has been studied and reported to be thickest on the posterior tongue and thinnest on the hard palate. In patients experiencing dry mouth, the film thickness on the hard palate was thinner than 10 µm [63]. When salivary flow is low, areas of the mucosa become desiccated, friable and much more susceptible to abrasion from foods, trauma from chewing and from ill-fitting dentures.

Dental decay

Xerostomia, or the subjective feeling of a dry mouth, is generally accompanied by hyposalivation. Normal saliva is a rich fluid containing electrolytes, buffers to neutralize oral acidity and antimicrobial proteins to counter *Streptococcus mutans,* which is the main bacteria associated with dental decay. Hyposalivation will mean fewer buffering and flushing opportunities for the oral hard tissues [64,65]. Lack of saliva may predispose to atypical dental decay observed on the cervical, incisal and radicular portions of the teeth [66]. Low salivary secretion promotes rapid formation of dental plaque. Due to early and often undetectable changes in salivary constituents that can promote tooth loss, it has been suggested that early dental loss may reflect a silent involvement of the salivary glands. Early changes in salivary biochemistry promoting dental decay may occur long before xerostomia [67,68].

Quality of life

Quality of life is profoundly affected due to diminished ability to eat, speak, sing, socialize, sleep and be a productive member of the work force. Hence, oral dryness in SS is more than an inconvenience. Reports have suggested that physicians and dentists do not appreciate the oral–systemic connection and the contribution of oral symptoms to quality of life [69–72].

Detection of food taste is aided by the chemical reaction between saliva, tastants and taste receptors. The sensation and sensitivity of taste may be altered with diminished saliva. Oral taste buds are located in the epithelial folds of the foliate and circumvallate papillae, and fungiform papillae and soft palate. Taste substances dissolve in the salivary fluid layer to reach and stimulate taste receptors. In addition, the epidermal growth factors in saliva may promote formation and renewal of taste buds. Low flow may affect food choices and compromise nutritional status [73].

Sjögren's syndrome patients show lower submandibular/sublingual flow rates and changed salivary composition of parotid and submandibular/sublingual saliva. Salivary changes make speech more difficult and may result in less willingness to engage in social interaction, and discomfort with interpersonal communications. A reduction of salivary volume will complicate formation of a food bolus for swallowing, creating difficult social situations [74]. In SS patients, halitosis can also be a concern. In patients with a low unstimulated salivary flow rate, clearance of bacteria and desquamated

epithelial cells is reduced greatly, increasing the tendency for halitosis. This may be especially problematic before breakfast as salivary flow is further reduced during sleep.

In a recent report of quality of life in a SS cohort, salivary flow rate was correlated significantly with both the Disease Damage Index published by Vitali *et al.* [75], and a standardized Oral Health Impact Profile (OHIP-14) [76]. The number of autoimmune symptoms was correlated with both oral and generic quality of life. Of note, oral health independently accounted for a significant percentage of variance in the generic Short Form-36 (SF-36) domains of general health and social function. The findings suggested that oral health has an independent influence on general quality of life beyond the effects accounted for by other autoimmune symptoms [72].

With increased awareness of the importance of oral health for patients with 'dry mouth', physicians can screen for oral disease, provide oral health education, initiate preventive and management strategies, and encourage patients to consult with their dentist for a complete oral evaluation.

Management of sequelae
Hyposalivation
The dental management for patients with SS is critical to their long-term oral health. While glandular damage cannot be restored, proactive management to increase oral lubrication is important. Management of oral manifestations includes intense oral hygiene, prevention and treatment of oral infections, use of saliva substitutes and local and systemic stimulation of salivary secretion. Cholinergic agents, such as pilocarpine and cevimeline, are helpful in patients with residual salivary function.

An important feature of having a continuous flow of unstimulated saliva into the mouth is that it reduces the probability that oral bacteria will be able to ascend the salivary ducts and create retrograde glandular infections.

Dental erosion & decay
As mentioned, patients demonstrating hyposalivation will also demonstrate increased susceptibility to dental decay. Enamel dissolution begins at a pH of approximately 5.5, but will vary depending on the concentrations of calcium and phosphate ions within the saliva. Fruit juices and carbonated drinks can be especially problematic due to the sugar content and acidic pH [77]. The pH of common colas is approximately
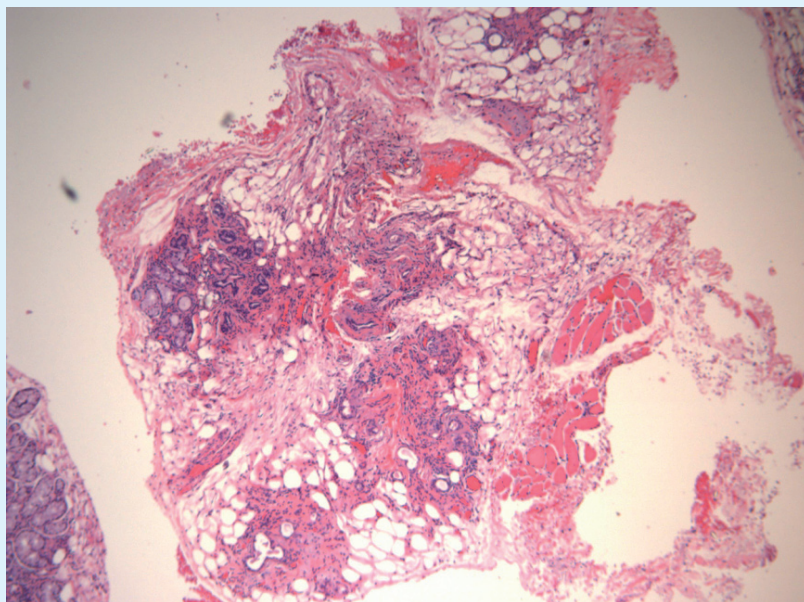

Figure 4. Labial salivary gland biopsy showing chronic sclerosing sialadenitis. Magnification: 5×.

2.5–3.4. Sports drinks and other beverages have been assessed as well. Coca-Cola® Classic produced the lowest mean pH, while Starbucks® Frappucino produced the highest pH of any of the drinks except for tap water. Red Bull had the highest mean buffering capacity (indicating the strongest potential for erosion of enamel), followed by Gatorade®, Coca-Cola Classic, Diet Coke® and Starbucks Frappucino [78]. Buffering capacity and frequency of drinking are also significant. Reduced residence times of beverages in the mouth by salivary clearance or rinsing would appear to be beneficial [79]. Frequency of drinking is more significant, in that buffering capacity cannot keep pace with the acidic insult. Dental erosion may also be caused by citrus abuse (sucking on citrus fruit or leaving citrus fruit in contact with tooth enamel for long periods) and the use of chewable vitamin C tablets. Dental erosion of the posterior teeth is an important finding with respect to the diagnosis of gastro-esophageal reflux disease (GERD). Reflux of acidic gastric fluids into the posterior part of the oral cavity can promote enamel dissolution. Therefore, it is important for physicians to evaluate patients exhibiting dental erosion for acid reflux disease [80,81].

Home care
Follow-up visits every 4 months may assist in monitoring and treating active dental caries. Patients should be educated and empowered to assist in the management of their own oral

health. Salivary stimulants such as sugar-free gums and lozenges will assist in enhancing the salivary flow and are readily available. Xylitol-sweetened gums and lozenges are beneficial due to their reported anticariogenic effects [82]. The choice of product to stimulate saliva depends on individual preference [22]. Efficacy will vary with frequency of use and the amount of functional salivary gland tissue. Artificial saliva substitutes and oral hygiene products that contain lactoferrin (e.g., Biotene® toothpaste and mouth rinse) will also be helpful [83]. Toothpastes should contain fluoride and be nonabrasive, to better protect the enamel. Sodium lauryl sulfate-free toothpastes might be preferred, as this compound has been associated with hypersensitivities.

Meticulous home care is critical and should include a customized fluoride program. For maximum protection, patients should brush and floss following all sugar exposures and seek dental care every 4–6 months to monitor caries status. Dentist-applied fluoride varnishes may deter progression of dental decay and decrease dentin sensitivity on exposed root surfaces. Topical fluoride gels, either brush-on or administered via custom-made carriers at bedtime, are important adjuncts for long-term dental health. Neutral sodium fluoride (1.1%) or 0.4% stannous fluoride have caries reduction activity, but large-scale controlled trials in Sjögren's patients have not been conducted to compare efficacy between the two agents. The most important time for tooth brushing is just before bedtime, because salivary flow is negligible during sleep and the protective effects of saliva are lost [28,84].

Sialogogues

In addition to xylitol-sweetened lozenges and gums, prescription sialogogues, such as pilocarpine and cevimeline, can be very helpful as long as functional salivary gland tissue remains. Studies have demonstrated objective improvement by increasing the rates of saliva and tear flow in SS patients, and/or subjective improvement of symptoms of dry mouth, dry eyes and overall dryness [85–89]. One study evaluated the efficacy of a hydrogel polymer buccal insert as a controlled-release delivery vehicle for pilocarpine. The authors found that the insert delivered more than 85% of a 5-mg dose of pilocarpine hydrochloride with minimal side effects [90]. Prescription sialogogues are not recommended for all patients. They should not be used in patients with uncontrolled asthma or narrow-angle glaucoma, and should be used with caution in certain types of cardiovascular disease and liver conditions.

Xerostomia-inducing medications

Approximately 400 medications can induce some degree of salivary gland hypofunction [91,92]. These will include diuretics, α-adrenergic agents and antihypertensive agents such as β-blockers, calcium-channel blockers and angiotensin-converting enzyme inhibitors [93]. Anti-anxiety drugs and appetite suppressants may be problematic as well. An important part of patient education concerns over-the-counter xerostomia-producing medications. Patients may be unaware that components of common antihistamines (pseudoephedrine) and sleep medications containing diphenhydramine hydrochloride will increase the severity of oral dryness.

Periodontal concerns

Not only are SS patients more susceptible to dental decay and *Candida*, but their periodontal status should be monitored as well. While some reports indicate no significant difference between the periodontal status of SS patients and controls [94–97], others report more severe periodontitis in SS patients [98,99].

Restorative dentistry & surgical procedures

Patients should be given all assistance possible to maintain their dentition in the optimal condition. This includes the preventive therapy described above, as well as conservative restorative therapy geared towards long-term function in an environment with probable salivary hypofunction. In some patients, SS will be accompanied by rheumatoid arthritis, resulting in a diminished ability to brush and floss teeth due to metacarpal/phalangeal changes and chronic pain. Periodontal therapy, fixed partial dentures and implant-supported prosthesis should be considered in conjunction with systemic health, and sustainable oral comfort and esthetics. As saliva will be compromised, adapting to conventional removable dentures is often unsuccessful. Implant-retained bridges and dentures have been extremely successful in SS patients, with proper patient selection.

As many of these patients are taking bisphosphonates for osteoporosis, the option of periodontal surgery, implant replacements for lost teeth and implant-supported dentures is one that should be approached with care and patient informed consent. While the potential

for bisphosphonate-associated osteonecrosis of the jaw in patients taking oral therapy is low, it is a concern. Concomitant prednisone or immunosuppressive therapy will put the patient in a much higher risk group. No consensus has been reached to date precisely quantifying the degree of risk associated with bisphosphonates and dental therapy. In an ideal situation, surgical dental care would be completed prior to initiation of oral bisphosphonate therapy. However, this is not always feasible. Ongoing routine dental care is necessary for all SS patients, and must not be discontinued due to bisphosphonate therapy. However, the potential of bisphosphonate-associated osteonecrosis should be reviewed with SS patients prior to dental care, especially periapical or periodontal surgery, extractions and implant placement procedures [100–105].

Candidiasis

Due to diminished concentration of antifungal proteins normally found in saliva and the lack of mechanical flushing action that saliva provides, oral candidiasis is a concern. When the oral balance is altered, antifungal defenses are overwhelmed, and *Candida* may flourish. *Candida albicans* has been isolated from dental plaque in SS patients at higher prevalence than control subjects (73 vs 7%) despite good oral hygiene [106]. In another report, the prevalence of oral *Candida* varied according to the methods used to determine the presence of the organism (49% positive with wet mount, and 77% positive with oral rinse cultures). A low stimulated salivary flow rate was associated with *Candida* carriage [107]. In another study, oral candidiasis was diagnosed in 74% of SS patients, versus 23% in the control group. Frequent symptoms were increased sensitivity to spicy foods (58%) and unpleasant metallic taste (40%). Common signs of oral candidiasis were erythematous lesions on the dorsum of the tongue (68%) and angular cheilitis (24%) [108]. If the patient complains of a 'burning tongue' and dysgeusia, oral candidiasis should be suspected. The incidence of oral candidiasis will increase with glucocorticoid-containing inhalers and systemic prednisone. Treatment includes topical antifungal therapy with nystatin oral suspension or tablets, or clotrimazole 10 mg oral troches four to five times per day for 2 weeks. For angular cheilitis, topical cream or ointment preparations applied to the commissures, in addition to tablets for intraoral topical treatment, is helpful. For persistent infections, systemic antifungal therapy such as fluconazole, 100 mg per day for 2 weeks, could be used.

When oral candidiasis is diagnosed, the patient should be instructed to purchase a new toothbrush in addition to appropriate topical or systemic therapy. Removable dentures frequently become infected with candidiasis and should be disinfected through vigorous brushing and soaking in commercial agents according to manufacturer's instructions. Patients should be discouraged from wearing the dentures at night-time during sleep. Cleansing dentures in a solution of 1% sodium hypochlorite, or if they contain exposed metal, in a 1:750 dilution of benzalkonium chloride, has been suggested [109].

Salivary gland enlargement & lymphoma

Salivary gland enlargement, which often starts unilaterally, but becomes bilateral, can be chronic or episodic. Enlargement may be due to SS-related nonspecific inflammatory changes, sialolithiasis and retrograde sialadenitis. Additional considerations for bilateral enlargement of the parotid and submandibular salivary glands include anorexia nervosa, bulimia, diabetes mellitus, hypothyroidism, alcohol-induced hepatic cirrhosis, HIV and hepatitis C [110–115].

When long-standing salivary gland enlargement in SS suddenly increases in size or pain, imaging and biopsy are recommended. The differential diagnosis would include sialolithiasis, salivary gland tumor, low-grade mucosa-associated lymphoid tissue (MALT) lymphoma and aggressive non-Hodgkin's lymphoma. Patients with SS have an increased risk of developing lymphoma [116–120]. Early literature reported that Sjögren's patients have a 44-fold increase in the rate of lymphoma [119], but more recent reports have lowered the prediction to a 16-fold increased risk [121]. These tumors may arise in the salivary gland or within lymph nodes. What was formerly considered a 'benign lymphoepithelial lesion' in the parotid gland might currently be diagnosed as a low-grade non-Hodgkin's B-cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma [122]. MALT is normally found in Peyer's patches in the ileum of the lower gastrointestinal tract, where it plays a role in normal humoral immune response. Mononuclear cell lymphocytic infiltrates in the exocrine glands can develop into marginal zone B-cell lesions or acquired MALT. A recent enlargement or persistent parotid enlargement [123] could be a lymphoma. MALT lymphomas have even been discovered though SS labial salivary gland biopsies [124]. Patients with SS have an increased risk of developing monoclonal B-cell MALT

lymphoma, perhaps due to prolonged autoimmune inflammation or persistent antigenic stimulation to virus or bacteria. Occasionally, high-grade lymphomas develop that can demonstrate aggressive behavior. In a cohort of 723 primary SS patients, one in five deaths was attributable to lymphoma. The presence of palpable purpura and low C4 levels at the first visit adequately distinguishes high-risk patients (type I primary SS) from patients with an uncomplicated disease course (type II [low-risk] primary SS) [125].

Imaging of a salivary gland enlargement is essential for diagnosis and treatment [126,127]. The role of imaging is to define location, detect malignant features, assess local extension and invasion, and detect nodal metastases. A lymphoma arising in the parotid gland has a clinical presentation similar to other neoplasms arising within the parotid gland. A CT scan is useful to determine the site and extent of the disease, loco-regional nodal status and contralateral gland and neck status. Multifocality and associated adenopathy are associated with, but not exclusive to, parotid lymphoma. Although poor tumor boundary definition on CT imaging is a strong predictor of malignancy, no pathognomonic finding specific for lymphoma has been identified.

For lesions arising in the superficial parotid and submandibular gland, ultrasound may be used for initial assessment. For lesions of the deep lobe of the parotid gland and minor salivary glands, MRI and CT are the modalities of choice. If deep-tissue extension is suspected or malignancy confirmed on cytology, an MRI or CT is mandatory to evaluate local invasion. For all tumors in the sublingual gland, MRI should be performed as the risk of malignancy is high [128]. Recently, a report on a proposed MR factor analysis using dynamic contrast-enhanced MRI on 35 salivary gland tumors indicated that the 2D distributions of the time–intensity curve (TIC) patterns correlated well with the histological features of the salivary gland tumors and allowed more detailed dynamic structures of tumors when compared with the results obtained by conventional dynamic study analysis [129].

Future therapies

Several potential therapies are in their early phases of utilization or undergoing active research. These include anti-T- and anti-B-cell therapies, gene transfer therapies and proteomics, with a focus on salivary biomarkers that may ultimately lead to new therapies.

Anti T- & B-cell therapies

The gain in knowledge regarding the cellular mechanisms of T- and B-lymphocytic activity in the pathogenesis of SS, and the current availability of various biological agents (anti-TNF-α, IFN-α, anti-CD20 and anti-CD22) have resulted in new strategies for therapeutic intervention. Currently, B-cell-directed therapies seem to be more promising than T-cell-related therapies. However, large, randomized, placebo-controlled clinical trials are needed to confirm the promising results of these early studies. When performing these trials, special attention must be paid to prevent the occasional occurrence of severe side effects [130]. Anti-TNF agents (infliximab and etanercept) and B-cell targeted therapies (rituximab and epratuzumab) have been used in primary SS. In a well-controlled, double-blind clinical trial, anti-TNF therapy, infliximab, was reported to be ineffective in SS [131]. Anti-B-cell therapy is a potential treatment for the glandular and extraglandular manifestations, including management of SS-associated lymphoma [132]. Anti-CD22 monoclonal antibody is expressed on the surface of normal mature and malignant B lymphocytes. It appears to be involved in the regulation of B-cell activation through B-cell receptor signaling and cell adhesion. It is complementary to the known effects and role of CD20 antibodies. It may provide distinct therapeutic benefits for autoimmune diseases [133].

A recent study suggested that mizoribine could be an effective treatment for primary SS. Mizoribine is a nucleoside produced by *Eupenicillium brefedianum* with antibiotic, cytotoxic and immunosuppressive activity. Improvements were noted in salivary flow and a physician's assessment of oral sicca symptoms, all measured using a 10-cm visual analogue scale [134]. One case has been reported with sudden onset of diabetic ketoacidosis and acute pancreatitis in a rheumatoid arthritis patient 2 weeks after introduction of mizoribine therapy [135].

Gene-transfer therapy

Research is being focused on implementing tissue-engineering principles combined with gene transfer and stem-cell methodologies to develop an artificial salivary gland device [136]. There is some optimism regarding restoring function to the damaged salivary gland [137]. Reports of experiments on animal models have revealed that the physical and biological characteristics of salivary glands provide unique advantages favoring successful gene transfer [138,139]. Considering such inherent advantages, the efficacy and safety

of applying gene transfer to salivary glands is believed to have extensive clinical value. The prospects seem promising to restore the salivary gland function by gene transfer to the gland *in vivo*.

Current clinical trials indicate that immuno-modulatory protein therapy can benefit patients with certain autoimmune diseases. The challenge to systemic protein therapies is ineffective administration routes and systemic side effects. An alternative approach being investigated is developing localized expression via gene therapy in the salivary glands. Genes encoding cytokines or cDNAs encoding soluble forms of a key cytokine receptor can be introduced directly into the salivary glands. The expected outcome is alteration of immune response locally, but not systemically. Several gene targets are being examined [140].

Proteomics

Recent developments in proteomics have resulted in the identification of a large number of different proteins, both in whole saliva and in secretions from individual glands. The technique uses an initial separation of proteins by means of electrophoresis or chromatography, isolation of small groups of proteins or their constituent peptides, and after further separation by means of chromatography, identification of the peptides via mass spectrometry. From a database of the peptides in known proteins, researchers can then identify the proteins present in saliva. Dr David Wong, of UCLA (CA, USA), has been a leader in this field. A recent study indicated that 16 proteins were downregulated and 25 were upregulated in SS patients compared with matched controls [141]. As the authors indicated, large-scale multicenter clinical trials must be completed before use in clinical settings can be moved forward. It is expected that these biomarkers will be used for monitoring severity or progression of dysfunction and response to treatments. Much must be done, but the future is optimistic.

Executive summary

Clinical signs & symptoms

- Clinical signs and symptoms may include xerostomia and hyposalivation dental decay, a desiccated, erythematous, fissured tongue, oral candidiasis and salivary gland enlargement.

Diagnosis

- Diagnosis will include subjective patient findings such as reported oral sicca, or the sensation of 'dry mouth' and positive responses to questions regarding oral dryness.

- Objective diagnostic findings may include lack of salivary pooling in the floor of the mouth, and diminished whole unstimulated salivary flow rate, salivary gland enlargement, positive imaging of the major salivary glands, and a positive labial salivary gland biopsy.

Management

- Management of oral manifestations will include supportive care such as salivary stimulants and oral lubricants, frequent dental visits with meticulous patient oral hygiene, a customized fluoride program and nutritional counseling. Due to the impact of oral manifestations on quality of life, patient education is important to empower patients to participate in their own care.

Future therapies

- Future therapies include anti-T- and anti-B-cell therapies, gene transfer therapies and proteomics.

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CME Oral manifestations of Sjögren's syndrome

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	1	2	3	4	5
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The activity was presented objectively and free of commercial bias.					

1. Which of the following is *least* likely to be a common manifestation of Sjögren's syndrome (SS)?
   - ☐ **A** Dry eyes
   - ☐ **B** Dry skin
   - ☐ **C** Dry mouth
   - ☐ **D** Fatigue

2. Which of the following *best* describes the prevalence of systemic extraglandular manifestations of SS?
   - ☐ **A** 20%
   - ☐ **B** 30%
   - ☐ **C** 40%
   - ☐ **D** 50%

3. SS is *least* likely to be associated with which one of the following conditions?
   - ☐ **A** Multiple sclerosis
   - ☐ **B** Rheumatoid arthritis
   - ☐ **C** Scleroderma
   - ☐ **D** Primary biliary sclerosis

4. Which of the following is *least* likely to be a criterion of the European–American Consensus Group for the diagnosis of SS?
   - ☐ **A** Ocular signs
   - ☐ **B** Salivary gland biopsy findings
   - ☐ **C** Presence of another autoimmune disease
   - ☐ **D** Presence of serum autoantibodies

5. Which of the following infections is of most concern in patients with SS?
   - ☐ **A** Oral herpes simplex virus
   - ☐ **B** Oral candidiasis
   - ☐ **C** Mumps virus
   - ☐ **D** Streptococcal B infection