Clinical Immunology 203 (2019) 81–121

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

Sjogren's syndrome: An update on disease pathogenesis, clinical manifestations and treatment

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1. Introduction/History

Sjogren's syndrome (SS) is one of the most common autoimmune diseases. It may exist as either a primary syndrome or as a secondary syndrome when associated with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and primary biliary cirrhosis [1–4]. The true prevalence of SS is very hard to determine because of frequent changes in diagnostic criteria, variation in the method of diagnosis based on the training of the clinician making the diagnosis (i.e. Ophthalmologist vs. Oral surgeon v Rheumatologist vs. Internist, etc.) and inclusion of novel diagnostic markers that are potentially more sensitive. While SS was once considered a rare disease, it is now considered the second most common autoimmune disease, after rheumatoid arthritis. Its prevalence is estimated at 1% (0.1 – 4.8%) with an incidence of 7 per 100,000 in the United States. It is felt that roughly 4 million Americans have SS with 90% of them being women and 50% of them having SS in association with another autoimmune disease [5–7]. The incidence of SS is felt to be lower in China and higher in Japan [8]. While SS is felt to be a disease predominantly of women, with a female to male ratio of 9:1, the incidence of SS is likely higher in males than is currently estimated, since males tend to make a different pattern of autoantibodies than females and are often missed with the current diagnostic criteria [9,10].

Dr Johann von Mikulicz-Rdeck, a surgeon from Cernowitz, Austria, is credited with identifying the first patient with Sjogren's syndrome in 1892 based on round-cell infiltrate and acinar atrophy of the parotid and lacrimal glands [4,11]. The syndrome is named, however, after an Ophthalmologist from Jonkoping, Sweden, Dr Henrik Sjogren, who in 1930 noted a patient with low secretions from the salivary and lacrimal glands. He subsequently published on a series of patients with "keratoconjunctivitis sicca" in 1933 and 1951 that brought the syndrome to worldwide medical attention [11,12]. He distinguished the primary disease from other causes of keratoconjunctivitis sicca, such as vitamin A deficiency and tuberculosis. In the 1950's and 1960's Sjogren's syndrome was felt to be a relatively rare disorder and the appreciation of its association with other autoimmune diseases was just starting [13]. In the 1970's, immunological abnormalities associated with Sjogren's syndrome, especially hypergammaglobulinemia, monoclonal gammopathiy and various lymphoid abnormalities were just being elucidated. The association between SS and lymphomas was noted, minor salivary gland biopsies were used for diagnosis, immunological therapies, such as the use of corticosteroids were attempted, the association of SS with HLA-B8 and DR3 was made, and animal models for SS were first examined [14–16]. In the 1980's came the association of SS with anti-SSA and anti-SSB antibodies [17]. In addition, SS was noted to have a strong correlation with chronic fatigue, cholinergic agents were used to increase salivary gland flow [18], immunological studies focused on the hypothesis that SS involves abnormal B cells and T cells of the adaptive immune system producing autoreactive antibodies and direct cytotoxicity [19], and genetic studies identified particular human leukocyte antigen (HLA) associations with SS [20]. The 21st century has seen a blossoming of research in SS that has led to improved understanding of

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https://doi.org/10.1016/j.clim.2019.04.009
Received 19 April 2019; Accepted 19 April 2019
Available online 29 April 2019
1521-6616/

clinical manifestations, greater appreciation of disease pathophysiology including the involvement of the innate immune system, role of epithelial cells and other cell types, determination of contributory genetic factors, development of improved animal models and therapeutic trials with encouraging outcomes. These are discussed in the remainder of this review.

2. Clinical manifestations

2.1. Oral manifestations and complications

2.1.1. Dry mouth

Sjögren's is often referred to as the "*sicca syndrome*" (from the Latin *siccus* meaning dry or thirsty) and xerostomia is one of its most prevalent symptoms.

Saliva is a chemically complex fluid containing over 2000 proteins and various glycoproteins, lipids, electrolytes, small molecules, specific salivary IgA's, hormones and buffers that all play a vital role in oral health [21]. It preserves the dentition and inhibits the growth of microorganisms; lubricates and protects the tongue and oral mucosa from trauma; facilitates taste, mastication, deglutition, speech and initiates carbohydrate digestion in the mouth [22,23]. Consequently, the oral signs and symptoms of SS extend far beyond those of simple dryness.

Patients may initially notice intermittent daily or nocturnal dryness or cotton mouth sensation that gradually becomes more prominent during the day. As the condition progresses Sjögren's sufferers eventually find themselves constantly drinking water. The mucosa becomes traumatized and mouth sores and/or oral discomfort develop. This may eventually lead to glossodynia or stomatopyrosis. The patient may describe an unpleasant taste in the mouth or dysgeusia with familiar foods. Food particles may stick to the gums and mucosa and, it may be difficult to chew and swallow dry foods without water. Eating becomes unpleasant and weight loss ensues. Cheilosis is present. Dry throat, hoarseness and dysphonia can also occur. The dryness may also progress to the point of disturbing sleep due to nocturnal fluid ingestion and nocturia. The lack of saliva may also cause downstream consequences in the gastrointestinal tract as described below [24].

2.1.1.1. Caries. Carious, chipped and broken teeth are among the most visible and costly dental complications of SS [25,26]. Like other xerostomic populations, Sjögren's sufferers frequently develop cavities in unusual locations including: root caries at or below the gingival margin, cervical caries in the neck of the tooth and cavities on the incisal surfaces [27]. Cervical lesions that extend circumferentially around the tooth neck eventually cause the tooth to fracture. Restorative work tends to be less successful in SS patients than other groups and many patients will eventually require partial or complete dentures. Unfortunately, this solution often fails to solve the problem since denture adhesion will be less than optimal without sufficient saliva [23].

2.1.1.2. Chronic erythematous candidiasis. The normal oral microbiota for most individuals includes *Candida albicans* and other Candida species [28,29]. Certain conditions or circumstances such as diabetes, antibiotic or steroid use, or xerostomia may predispose to Candida overgrowth and pathogenicity. Patients typically complain of stomatopyrosis or intolerance of acidic or spicy foods. Findings may include angular cheilitis, atrophy of the filiform papillae and mucosal erythema. In chronic cases the tongue may also develop an erythematous, cobblestoned appearance. The classic findings of pseudomembranous candidiasis occur less frequently. The overgrowth of Candida may further contribute to the patient's lack of pleasure from eating and poor oral intake.

2.1.2. Major salivary gland swelling

Acute, intermittent or chronic persistent swelling of the parotid or submandibular glands may be unilateral or bilateral and observed in up to 30% of SS patients. This swelling can be the presenting manifestation of the disease or occur at any point during the course. Patients who present with acute glandular swelling associated with fevers and facial erythema are presumed to have acute bacterial sialadenitis until proven otherwise. An attempt should be made to milk the involved gland and culture the exudate from Stenson's or Wharton's duct. An individual who develops salivary gland swelling after eating or chewing most likely has obstructive symptoms due to sialolithiasis or sialostenosis with mucus plugs. When the swelling begins to subside patients may be aware of passing stones or gravel in the mouth or experiencing a sour taste from a mucus plug. Intermittent or persistent salivary gland swelling may also be due to inflammatory sialadenitis from lymphocytic infiltration of the major salivary glands and is typically responsive to steroids and other immunosuppressives. Sjögren's patients on chronic or frequent intermittent corticosteroids or with metabolic disorders sometimes develop sialadenosis or fatty infiltration of the glands. Any individual with persistent glandular swelling despite prolonged therapy (e.g. > 12 weeks) or whose salivary glands feel indurated or nodular should undergo imaging and/or a major salivary gland biopsy to rule out non-Hodgkin's B-cell lymphoma.

2.2. Spectrum of ocular disease

Dry eye, or keratoconjunctivitis sicca (KCS) is the most common ocular manifestation of SS [30]. As such, management of Sjögren's is heavily focused on ocular surface rehabilitation. However, SS can also lead to other serious vision-threatening ocular complications including corneal melts [31], uveitis [32], scleritis [33], and optic neuritis [34,35] as detailed below.

2.2.1. Tear film

The tear film is critical for maintaining the health of the ocular surface. It coats the cornea and conjunctiva and serves to maintain optical clarity, prevent bacterial overgrowth, prevent epithelial breakdown, and serves as a barrier against environmental hazards [36]. The tear film consists of three main components: the aqueous layer, lipid layer, and mucin layer [36]. The aqueous layer comprises the largest component and is produced by both the primary lacrimal gland and accessory lacrimal glands. The meibomian glands located in both the upper and lower eyelids produce the outer lipid layer, which stabilizes the tear film and limits the evaporation of tears. Finally, the mucin layer is secreted by the corneal and conjunctival epithelium, as well as goblet cells within the conjunctival epithelium and helps tears adhere to the ocular surface. The mucin layer is a glycocalyx formed primarily by high molecular weight glycosylated membrane-associated mucins such as MUC1, MUC4, and MUC16 [37]. These mucins interact with galectin-3, an important signaling protein that helps prevent pathogen entry into the eye; mucins also decrease friction of the ocular surface during blinking [37]. Abnormalities in the any of these three layers can lead to an unstable tear film and dry eye disease.

2.2.2. Mechanism of dry eye

A comprehensive assessment by a skilled eye care provider is necessary to determine the primary cause(s) of dry eye. SS has classically been associated with aqueous tear deficient dry eye [30] but there is evidence that meibomian gland dysfunction (MGD) also plays a role [38]. Sjögren's can cause destruction of both the primary and secondary lacrimal glands via T cell-mediated inflammation [30] with resultant hyposecretion of tears. Decreased tear production can easily be detected on clinical exam using the Schirmer test. A result of less than 10 mm/ 5 min. indicates decreased tear production [39]. Vital dyes such as fluorescein and lissamine green are also used to assess the severity of ocular surface damage.

With MGD, there is decreased expression of the lipid layer onto the ocular surface with resultant tear film instability and evaporative dry

eye. This can be detected on clinical examination by inspection of the eyelids with biomicroscopy, direct visualization of the meibomian glands using infrared imaging (meibography) or by performance of a fluorescein tear film break up time (TBUT) [38]. In this test, following the instillation of fluorescein into the eye, the patient blinks once, then holds the eye open while the number of seconds is counted until the fluorescein starts to disappear. A value greater than 10 seconds is normal and the lower the value on TBUT the more severe the evaporative dry eye [38].

2.2.3. Dry eye signs and symptoms

Among patients with SS, dry eye is one of the most prominent clinical features [40,41]. Other common symptoms include a burning sensation, grittiness, itching, redness, mucus exudate, photophobia and glare [42]. Symptoms often worsen throughout the day, and patients experience transient episodes of blurred vision that improve with blinking or resting the eyes. Conditions that exacerbate evaporation from the eye such as air conditioning, heaters, low humidity, or wind will further worsen KCS. Additionally, activities that require concentration such as reading, watching TV, or using the computer may also aggravate symptoms due to decreased blinking and increased evaporation from the ocular surface [39]. In its earliest stages, KCS may cause mild discomfort. However, as the disease progresses it may cause severe pain, damage to the ocular surface, and chronic visual impairment. As a result, KCS can significantly impact activities of daily living as well as work productivity, and as such, many patients report a reduced quality of life [42]. Patients with concomitant MGD (posterior blepharitis) may experience increased burning, itchiness and foreign body sensation of the eyes along with redness, swelling and/or crusting and of the eyelids [39]. Occasionally, Sjögren's KCS may also be misdiagnosed as allergic conjunctivitis because of itchiness and other overlapping symptoms [43].

2.2.4. Corneal neuropathy

Although the clinical signs of dry eye may be similar between SS and non-SS dry eye patients, individuals with SS often complain of more severe symptoms such as burning, chronic pain and photo allodynia [44]. This phenomenon may be due in part to the presence of a corneal neuropathy [45]. In patients with SS, corneal nerves exhibit altered corneal morphology (e.g. tortuosity, decreased density, abnormal branching) and increased dendritic cell density that can be detected with *in vivo* confocal microscopy [44,45]. Regardless of the etiology of the corneal neuropathy, the change in morphology is associated with an increase in symptoms. Even in the absence of clear signs of dry eye on slit lamp exam, many patients will experience a phenomenon known as “pain without stain” [46]. When symptoms exist in the absence of clinical signs such as ocular surface staining, further testing with confocal microscopy is indicated [44,45].

2.2.5. Complications of KCS

Untreated, dry eye disease can be extremely detrimental. The tear film is responsible for a significant portion of the refractive power of the eye, and as such an irregular tear film will distort the patient's vision [42]. In addition, desiccation of the ocular surface can lead to epithelial breakdown. Without a healthy tear film or corneal epithelium, the eye is also at risk for the development of bacterial and fungal infections that can lead to corneal ulcers. Due to the severe inflammation on the ocular surface in patients with KCS, sterile, or non-infectious, corneal ulcers may also form. These ulcers can lead to corneal melting and, in severe cases, perforation [31], and endophthalmitis.

Another disabling complication of moderate-severe dry eye disease is *filamentary keratitis*. In this condition strands of mucus and proteinaceous debris from shed epithelial cells remain attached to the corneal surface [40]. With each blink, the filaments are disturbed and cause severe pain, foreign body sensation, photophobia, and decreased vision. When filaments are removed either spontaneously or intentionally by a clinician, they may leave a residual epithelial defect that becomes a potential nidus for infection. Additionally, removal of the filaments only provides temporary relief as recurrence is frequently observed. N-acetylcysteine eye drops may be used to help break down filaments in conjunction with aggressive surface lubrication or use of a bandage contact lens [40]. When this problem becomes chronic, filaments can fuse into large mucous plaques that may be recalcitrant to conventional therapies [40].

Because of the abnormal tear film in patients with SS, special considerations must be made when considering manipulation of the ocular surface. Notably, there have been many reports of sterile corneal melts that may lead to perforation following routine cataract, corneal, and refractive surgeries in SS [47–49]. Therefore, treatment of KCS must be optimized before consideration of such procedures. Contact lenses should also be used with caution in SS as patients are at higher risk for worsening dryness or bacterial or fungal keratitis due to the irregular nature of the ocular surface [50].

2.2.6. Ocular morbidities beyond dry eye

In addition to KCS, SS can also cause a myriad of ophthalmic complications. SS has been associated with both anterior and posterior uveitis both of which may present with pain, photophobia, floaters, and decreased vision [32,51]. Additionally, anterior uveitis and scleritis [33] both cause ocular redness in patients with primary SS. Scleritis must be diagnosed in a timely and accurate manner since failure to promptly treat may lead to scleral perforation, a sight and globe-threatening complication. Demyelinating conditions such as optic neuritis and neuromyelitis optica (NMO) have also been associated with SS [34,35,51]. In optic neuritis, patients complain of decreased vision, decreased color saturation, and pain with eye movement. These symptoms require aggressive treatment with high dose oral or intravenous steroids [51]. NMO is a more severe condition characterized by optic neuritis in association with longitudinally extensive transverse myelitis and is even more challenging to treat [51,52].

In conclusion, SS causes dry eye secondary to the autoimmune destruction of the lacrimal glands leading to aqueous deficient dry eye, which is commonly exacerbated by concomitant meibomian gland dysfunction. Dry eyes can predispose the ocular surface to vision-threatening complications such as corneal melting, ulcers, and perforations. Regular vigilance for other ophthalmic manifestations of SS such as uveitis, scleritis, and optic neuritis is equally important.

2.2.7. Other sicca symptoms

Since exocrine glands exist throughout the body other xeroses and/or complications thereof may include xeroderma, chronic pruritus, xeromycteria, epistaxis, dry ears, itchy ears, xerotrachea, cough, vaginitis sicca and dyspareunia. The latter symptoms may lead to sexual dysfunction, decreased activity and decreased sexual satisfaction in SS [53].

As observed with the eyes and mouth, decreased moisture of other mucosal surfaces in Sjögren's may also predispose to infections in these areas as well.

2.3. Systemic manifestations

2.3.1. Fatigue and other constitutional symptoms

Fatigue is the most common symptom in SS after dry eye and dry mouth, occurring in ~70-80% of patients [54–56]. Though it is common, it is poorly understood [57]. The pathogenesis is unknown and research thus far suggests that it is something intrinsic to SS without a clear etiology [54,55,57,58]. Though that may be true for SS in general, for any given patient with SS, the cause of fatigue may be multifactorial with potential contributors including poor sleep (owing to sleep apnea, restless legs, frequent awakening due to pain, and/or nocturia), depression, anxiety, fibromyalgia, anemia, hypothyroidism, dry mouth, and other reasons.

As the cause of fatigue in SS is unknown, it is perhaps not surprising that its management is often challenging with underwhelming results. Fatigue in SS tends to persist over time. One prospective study showed that it did not change significantly over a 5-year period [54]. One cohort study of 160 SS patients showed by multivariate analysis that depression, fibromyalgia, and the personality trait of neuroticism were all independent contributors to fatigue in SS and the authors thus recommend collaboration with behavioral health specialists to treat this problem [58]. Though studies have shown that cytokines and other markers of inflammation are not associated with fatigue in SS [57], one small double-blind, placebo-controlled, randomized pilot study demonstrated modest efficacy of rituximab in reducing fatigue [59]. However, given its high financial cost, potential side effects, and lack of strong evidence, rituximab is not recommended for fatigue in SS treatment guidelines [60,61].

Fevers may also be a prominent manifestation of SS and, in most large cohorts, occur in 6-13% of patients [62–64] at the time of initial evaluation. They may be low grade and inconsequential or sometimes more severe and associated with other constitutional symptoms including malaise, asthenia, worsening fatigue or a flu-like illness. Fevers in SS can be the presenting manifestation of the disease [62,65] or occur later in the course [62,63]. Persistent fevers associated with weight loss and/or night sweats should always prompt evaluation for an occult lymphoma.

2.3.2. Musculoskeletal manifestations

As with fatigue, articular manifestations are very common in SS with arthralgias occurring in ~50 to 75% [62,66,67] and arthritis (synovial inflammation) in ~10-30% [62,66–69]. The most common pattern observed is polyarticular and symmetric although monoarthritis has been observed. Signs and symptoms mainly involve the PIP, MCP, and wrist joints though other joints can be involved as well [67,68,70]. The onset of articular manifestations in SS is variable. One study of 419 SS patients followed for a mean of 76 months reported that joint symptoms started before sicca symptoms in ~20%, simultaneously in ~50%, and after sicca in ~30% [67].

For any given SS patient with arthritis, it may be difficult to determine whether the arthritis is due to SS alone or to concurrent rheumatoid arthritis (RA) since both have the same pattern of joint involvement. The inflammatory arthritis of Sjögren's however is, in most cases, nonerosive. An elevation in rheumatoid factor (RF) testing is characteristic of RA and is present in ~75% of RA cases; however, it is also present in ~60-70% of SS cases and is therefore not helpful in distinguishing one disease from the other [71]. Anti-cyclic citrullinated protein antibodies (ACPA), on the other hand, are elevated in a similar percentage of RA patients but in only ~10-15% of SS patients and therefore may be useful in predicting the development of RA in those with SS [71]. They do not, however, permit the differentiation of one disorder from the other as one cohort study showed that among 16 SS patients with +ACPA, almost half developed RA after a median follow up period of 8 years [71].

For any given SS patient with arthralgias, it may be difficult to distinguish between pain due to SS alone or pain due to concurrent fibromyalgia as both have many overlapping features. Fibromyalgia is a syndrome characterized by chronic widespread musculoskeletal pain, chronic fatigue, disturbed sleep, and myriad somatic symptoms that is felt to be associated with dysregulation of pain processing in the central nervous system. Though its prevalence in the general population is only ~2%, fibromyalgia has been noted in ~10-30% of patients with SS [55,72–74]. In SS patients with concurrent fibromyalgia, medications such as duloxetine or pregabalin may be preferred over immunosuppressive medications to treat joint pain.

In addition to the joints, the muscles can also be affected in SS. Up to 70% of SS patients may complain of myalgias [75]. Weakness can occur from hypokalemia as a result of renal tubular acidosis as noted in the renal manifestations section of this chapter. Weakness in SS can also occur from inflammatory myopathy. The frequency of inflammatory myositis in SS is quite rare and felt to occur in < 2% [62,69,76]. It is often subclinical or mild compared to polymyositis and dermatomyositis and presents in a nonspecific fashion, sometimes with mild weakness, myalgias, or no symptoms at all and, typically, with lower elevation in creatine kinase than that observed in these other disorders [75].

2.3.3. Hematologic abnormalities

The hematologic manifestations of SS can be separated into cellular and humoral components. The main cellular abnormalities, cytopenias, although more closely associated with systemic lupus erythematosus (SLE) are quite common in SS and can even be the presenting feature [77,78]. Humoral manifestations include hypergammaglobulinemia, hypogammaglobulinemia, monoclonal gammopathy, cryoglobulinemia, and elevations in autoantibodies. Although the hematologic manifestations found in SS are typically mild and clinically silent, several are prognostic markers for the development of lymphoma and increased disease mortality [62,69,79–82].

2.3.4. Anemia

Cytopenias are found in 30-60% of SS patients, with bi-cytopenias in 5-10%, and pancytopenia in only 1% [66,69,79,83]. The anemia of chronic inflammation most commonly occurs and is found in about 15-45% of patients depending on the series and definition of anemia [62,68,69,79]. Typically, it is mild and with no identifiable cause outside of the SS itself [79]. Other forms such as hemolytic anemia (1%), aplastic, pernicious, myelodysplastic, and pure red cell aplasia have also been reported in SS but rarely occur [69,79]. One Spanish series of 380 consecutive patients with primary Sjögren's syndrome (pSS) noted that 93% of anemias were normochromic and normocytic with only 4% microcytic and 3% macrocytic [79]. Severe anemia (defined by a hemoglobin level < 9 mg/dL) was infrequent and, found in only 4% of pSS patients [79]. It is important to note that anemia can also develop as a late complication of the disease. This was demonstrated in a Greek series of 536 pSS patients followed for a median of 31 mo. [69]. At the time of diagnosis 28.5% of subjects had anemia while another 16.4% developed it during the follow-up period [69]. Anemia in SS has been associated with a positive ANA (86% vs 70%), positive SSA/SSB (OR 2.6, 95% CI 1.5 - 4.4), higher focus scores on lip biopsies, and with peripheral neuropathy (22% vs 4%, p = 0.001) [68,69].

2.3.5. Leukopenia

Leukopenia has been observed in 10 to 25% of patients with SS [62,69,79,83]. One series reported that more cases were related to the effect of drugs or toxins than the disease itself [69]. Leukopenia in pSS is predominantly mild with only 0.2% of all patients having a white blood cell count less than 2000 cell/mm3 [79].

When considering the white blood cell differential in SS, neutropenia is noted in roughly 5 to 30% [69,79,83,84], lymphopenia in about 10% [69,79,83], and eosinophilia in 12% [79]. Neutropenia is associated with an increase in hospital admissions due to infections (24% vs 9%, p = 0.002), especially in those with a neutrophil count less than 1000/mm^3 as noted in one Spanish series of 300 pSS patients [84]. Severe neutropenia, as defined by a neutrophil count of less than 500/mm^3, is quite rare, found in only 2% of patients in the same series [84]. The presence of neutropenia in SS patients has been associated with the development of lymphoma [69] as has the presence of CD4+ T-cell lymphopenia [82]. Other statistically significant hematologic associations in SS include the following: neutropenia with positive SSA/B (53% vs 22%), neutropenia with low C4 (17% vs 8%) [84], leukopenia with positive SSA and RF [68,79], and lymphopenia with renal involvement (13% vs 3%) [79].

2.3.6. Thrombocytopenia

Thrombocytopenia is noted in 5 to 13% of SS patients

[62,68,69,83]. As with anemia and leukopenia, it is usually mild [79]. Moderate thrombocytopenia (< 100 K/mm^3) is found in 3% of SS patients and severe thrombocytopenia (< 50 K/mm^3) in only 0.4% [79]. Interestingly, a Chinese series of 131 consecutive hospital admissions for severe thrombocytopenia (platelet count < 20 K/mm^3) found that of those due to an underlying connective tissue disease, the most common was pSS (53.7% of thrombocytopenia cases) followed by SLE (40.5%) [85]. Thrombocytopenia in SS has been shown to have statistically significant associations with renal disease (15% vs 5%), positive SSB (40% vs 25%), and positive minor salivary gland biopsy (OR 4.6, 95% CI 1.2 - 39.7) [68]. It is postulated that the etiology of thrombocytopenia in SS is due to anti-platelet antibodies and or immune complex mediated destruction [82].

2.3.7. Hyper- and Hypogammaglobulinemia

SS is characterized by lymphocytic infiltration of involved organs and polyclonal B-cell hyperactivity. This is reflected by some of the humoral abnormalities found in SS such as hypergammaglobulinemia which may occur in about 20-50% of patients [62,68,69,79]. Not surprisingly, hypergammaglobulinemia also correlates with higher focus scores on salivary gland biopsies [68]. Interestingly, hypergammaglobulinemia is one of two lab tests that have been shown to be predictive of the development of SS in those in whom the diagnosis is suspected [86]. This was demonstrated in a group of 830 subjects who did not meet 2002 American European Consensus Group (AECG) classification criteria for SS but in whom some objective findings of SS were present (e.g. Schirmer test of < 5mm/5 min.). Those with hypergammaglobulinemia at study entry were 4 times more likely to meet AECG classification criteria upon follow-up 2-3 years later than those with normal immunoglobulin levels (95% CI 1.5 - 10.1, p = 0.006) [86]. Hypergammaglobulinemia is also associated with an increase in the erythrocyte sedimentation rate (ESR) as seen in about 20% of SS patients [79]. Severe ESR elevations with levels greater than 100 mm/hr. are rare and found in only 4% of SS patients [79]. Though elevated immunoglobulin levels are not unexpected in SS, hypogammaglobulinemia has been noted in about 5- 15% [69,79]. In one series this finding was observed in 4 of 8 SS patients who developed lymphoma [79]. In the same series, immunodeficiencies were rare, found in only about 1% of SS patients, (CVID in 2 and IgA deficiency in 1) [79].

2.3.8. Monoclonal gammopathy

Monoclonal immunoglobulins have been observed in about 10- 20% of patients [79,80,83]. IgG is the most common isotype followed by IgM [80]. IgA and free light chains have also been reported [80]. Many of the monoclonal immunoglobulins found in SS are cryoglobulins which, in turn, have been found in about 10- 20% of patients [62,66,69,79,81,83,87]. The most frequent type of cryoglobulinemia in SS is a mixed monoclonal IgM with polyclonal IgG [81,87]. Monoclonal immunoglobulins in SS have been associated with pulmonary manifestations (25% vs 8%, P = 0.034) and hematologic malignancies (12% vs 1.6%, p = 0.004; OR 8.13, 95% CI 1.6 - 51.5) [80]. Cryoglobulinemia in particular is an important marker of systemic involvement and poor prognosis in SS. Its presence has been associated w/ cutaneous vasculitis (56% vs 8%, p < 0.001) [87], hypocomplementemia (75% vs 2%, p < 0.001) [87], and glomerulonephritis [69,81,88]. More importantly, cryoglobulinemia is a risk factor for developing lymphomas. This was demonstrated in a prospective Greek study completed over a 5-year period of 103 pSS subjects who at baseline were tested for cryoglobulinemia and had no known lymphoma [81]. Over the 5-year period, 7 subjects (6.8%) developed B-cell lymphomas. Six of the 7 (86%) who developed lymphoma had baseline cryoglobulinemia compared with 12 of 96 (12.4%) who did not develop lymphoma, thus indicating that the presence of cryoglobulinemia was a moderate risk factor for lymphoma development (r = 0.421, p = 0.0009).

2.3.9. Antiphospholipid antibodies

In SLE high levels of anti-phospholipid antibodies (aPL) are associated with an increased risk of fetal loss and venous and arterial thrombosis. Abnormal aPL results have also been found in 13-38% of SS patients, though mostly at low to moderate titers. These aPLs were associated mainly with hypergammaglobulinemia but not with thrombosis or fetal loss [79,89]. This suggests that the presence of low to moderate titer aPLs seen in SS may simply occur as an epiphenomenon of polyclonal B cell activation [89].

2.3.10. Hypocomplementemia

In addition to immunoglobulins, the other humoral component to consider in SS is complement. Low levels of C3 are reported in about 10-15% [66,68,69,83] of SS patients and low levels of C4 in about 5-20% [62,66,68,69,83]. In some cases, this may reflect disease activity related to consumption of complement from immune complex formation. Low C4 levels have been found to be associated with higher focus scores on minor salivary gland biopsy [68] and lymphomas [69]. In addition, similar to hypergammaglobulinemia, hypocomplementemia has been found to help predict the diagnosis the SS. As mentioned above, among 830 subjects who met some but not all of the 2002 AECG classification criteria for SS, those with hypocomplementemia at study entry were 6 times more likely to meet AECG classification criteria upon follow-up 2-3 years later than in those with normal immunoglobulin levels (95%CI, 1.8-20.4, p = 0.0004) [86].

2.3.11. Lymphoma

As Sjögren's syndrome is a disease characterized by B-cell hyperactivation, it is not surprising that those with SS have an increased risk of developing non-Hodgkin's B-cell lymphoma. The relative risk had been estimated to be 15-20 times that of the general population [90–92] but more recent studies suggest that this may be an overestimation [90,93–97]. The pathogenesis has been recently reviewed [90]. The most common type of lymphoma found in SS is a low-grade B-cell non-Hodgkin lymphoma (NHL) of the marginal zone histologic type, especially those of mucosa-associated lymphoid tissue (MALT) [90]. Other, less common subtypes include lympho-plasmacytoid lymphoma and, diffuse large B-cell lymphoma which is more aggressive and sometimes develops as a transformation from a low-grade subtype [90].

The lifetime risk of developing NHL in SS is felt to accumulate with time and has been estimated at 5-10% [90,93,98]. It tends to occur wherever SS happens to be active which is most commonly in the parotid and submandibular glands but can also be in the lymph nodes, orbits, nasopharynx, stomach, thyroid, and lungs [90]. The course tends to be indolent with a small tumor burden, normal LDH, and without B-symptoms, such as fever, weight loss or night sweats, in the majority (~75%) of patients [90].

There are various clinical and laboratory factors that may help predict the development of NHL in SS. The most consistent NHL predictors in the literature include parotid enlargement, lymphadenopathy, palpable purpura, low C4 complement level, and the presence of cryoglobulinemia [98]. Other, less consistent NHL disease predictors include splenomegaly, low C3 complement level, lymphopenia, neutropenia, and a monoclonal component in the serum or urine [90,98]. More recently reported predictors include elevated rheumatoid factor level [93,99], a focus score of greater than 3/4 mm^2 or the presence of ectopic germinal center-like lesions on minor salivary gland biopsy [98,99], and increased overall systemic activity with an ESSDAI score of greater than or equal to 5 [93]. The presence of multiple risk factors is felt to confer a greater risk of developing NHL [98].

Although lymphoma most frequently presents as persistently swollen parotid glands, it is important to note that parotid enlargement is common in SS and may be due to autoimmune inflammatory sialadenitis, infection, obstruction, or other causes. When due to NHL, it is more typically unilateral, persistent, and sometimes indurated and

nodular [90]. In addition to careful history taking and examination, imaging with an MRI scan and/or ultrasound may be helpful in the evaluation [90]. Biopsy confirmation is necessary whenever the diagnosis is in doubt or lymphoma is suspected. Lymphadenopathy is also fairly common in SS and noted in 8-32% [62,68,83]. Splenomegaly is less common and was observed in 7% according to one series [62].

The prognosis of NHL in SS is typically good, especially with the MALT subtype. For example, one retrospective study of 53 cases noted a 3-year survival of 97% and event-free survival of 78% [90]. When higher grade lymphomas occur, however, mortality rates can be significantly higher [100,101].

2.3.12. Gastrointestinal manifestations

There are variety of gastrointestinal (GI) manifestations that have been described in SS. These may occur due to lymphocytic infiltration of the GI mucosa or exocrine glands, autonomic neuropathies or the development of associated autoimmune diseases that occur with increased frequency in SS. Rarely vasculitis of the gastrointestinal tract may also occur.

2.3.13. Esophageal

Dysphagia, often described as the feeling of food getting "stuck" in the throat or chest, is a common complaint among SS patients. One case control study noted dysphagia in 65% of those with pSS compared with 3% of controls ($p < 0.01$); esophageal symptoms were noted in 80% and pharyngeal symptoms in 45% of SS subjects [102–104]. Numerous causes have been identified including esophageal dysmotility, esophageal webs, Zenker's diverticula, achalasia, reflux and lack of saliva flow [105–108]. When empiric treatment fails, evaluation with an upper endoscopy, barium swallow with video esophagram and, occasionally, esophageal manometry may be necessary.

Gastroesophageal reflux (GER) also commonly occurs in SS and may cause or contribute to various symptoms including: heartburn, hoarseness, chronic cough, nausea, chest pain and dysphagia. The same case control study mentioned above noted a GER prevalence of 60% in pSS patients compared to 23% in controls ($p < 0.01$) [103]. A cross-sectional population-based study in Taiwan found the risk of GER to by 2.4 times greater in 4650 SS patients than controls after adjusting for age, sex and comorbidities [109]. Potential contributors to GER in SS may include diminished saliva, decreased esophageal motility, sphincter relaxation, delayed gastric emptying time, or side effects of medications [109]. One study noted a delay in clearance of acid from the esophagus in SS patients with GER and suggested dysmotility as a cause [110]. Additionally, in SS the acid neutralizing capacity of saliva is diminished due to altered pH and decreased volume. Secretion of epidermal growth factor by the submandibular glands which inhibits gastric acid production may also be decreased [111,112].

2.3.14. Gastric

Common gastric complaints among SS sufferers include nausea, dyspepsia and epigastric pain [113]. The incidence of chronic atrophic gastritis is higher in SS than normal controls [114] and may be associated with altered mucosal function, hypochlorhydria, achlorhydria, hypopepsinogenemia and hypergastrinemia [113,115–117]. Biopsy studies typically show mononuclear cell infiltration of the mucosa and glandular atrophy with varying degrees of intestinal metaplasia [113,118]. Although *Helicobacter pylori* infection and anti-gastric parietal cell antibodies occasionally occur in SS the significance of these findings remains unclear [102]. In one study the eradication of *H. pylori* infection failed to improve dyspepsia and/or tissue atrophy in those with SS [119]. *H. pylori* infection, like SS, is a known risk factor for MALT lymphoma, although, at the present time, there is little evidence to suggest that having both *H. pylori* and SS confers an additive lymphoma risk [120].

Dysautonomia has been described in SS and may affect the gastrointestinal tract.

Two small studies prospectively evaluated autonomic dysfunction in at risk SS cohorts and reported a prevalence of gastroparesis ranging from 29-53% [121,122]. One study suggests that dysmotility in SS could be due to autoantibodies that may inhibit muscarinic receptor-mediated cholinergic neurotransmission [123]. This diagnosis should therefore be considered in any SS patient with chronic nausea, vomiting, anorexia, early satiety or weight loss in whom a prior upper endoscopy is normal.

2.3.15. Intestinal

Chronic diarrhea in Sjögren's syndrome has been described in up to 9% of patients [124] and represents a complex diagnostic challenge. Biopsy-proven celiac disease may occur in SS but prevalence seems to vary in different populations. Two studies reported the presence of biopsy-proven celiac in 4.5-15% of patients with SS [125,126] compared with the general population (0.5%); however, other studies have shown contrasting results with 0.9% of 114 patients in one study and 0% of 400 patients in another [63,127]. Hypersensitivity to certain foods in the absence of proven celiac disease may also aggravate symptoms such as bloating and diarrhea. One study reported improvement of gastrointestinal symptoms and arthralgias with dietary restriction of foods to which hypersensitivity was demonstrated. This was followed by a recurrence of symptoms upon re-challenge with the offending foods [128]. Systemic secretagogues (e.g. cevimeline, pilocarpine) that are used to treat xerostomia and other sicca symptoms may cause diarrhea and other GI symptoms related to cholinergic side effects especially when used at higher doses. Likewise, the excessive use of lozenges for dry mouth that contain xylitol or sorbitol as the artificial sweetener can also cause flatulence, bloating and diarrhea. Other rare causes of diarrhea in SS patients may include concomitant inflammatory bowel disease [129,130], small intestinal bacterial overgrowth syndrome (SIBO) [131,132] or lymphocytic colitis [133].

Vasculitis involving the GI tract in SS is uncommon and only documented in about 13 case reports to date [102,134]. It is frequently associated with cryoglobulinemia [102]. Although quite rare, this diagnosis should be considered in any SS patient with severe abdominal pain, GI bleeding, infarcted bowel or perforation.

Constipation occurs in SS more frequently than diarrhea and may result from lack of saliva flow or dysmotility. One small Scandinavian study noted that bowel symptoms were found more frequently in SS patients than controls including constipation (23% vs 3%), incomplete rectal emptying (27% vs 7%), and abdominal pain (27% vs 3%, all $p < 0.05$) [135].

There has been a lot of interest lately in the role that intestinal microbial composition plays in health and disease. Abnormal intestinal microbiota, also called dysbiosis, has been associated with autoimmune diseases including SS [136]. One small study demonstrated that severe dysbiosis was more prevalent in SS patients than controls (21% vs 3%, $p = 0.018$) and was associated with higher disease activity (ESSDAI 13 vs 5, $p = 0.049$) [136].

2.3.16. Pancreatic

Most pancreatic involvement in SS relates to pancreatic exocrine insufficiency and is typically asymptomatic; altered pancreatic function has been found in 36-63% of patients and varies depending on the method of evaluation [102,137–140]. Acute pancreatitis is mentioned in some series but is rare. The clinical diagnosis of chronic pancreatitis is also uncommon in SS [102]. One large series noted that chronic pancreatitis was present in less than 2% of pSS patients [102,141–143] whereas another found it in ~5% of those with autoimmune disease [144]. Several unusual cases dating back to the 1970's describe a triad of sclerosis cholangitis, chronic pancreatitis and SS [142,145]. The majority of these cases were male, and many had salivary gland swelling in addition to sicca symptoms. Since chronic pancreatitis is a prototypical manifestation of IgG4 related disease [146], this diagnosis must always be excluded before chronic pancreatitis and other

symptoms can be attributed to SS.

2.3.17. Hepatic

Liver enzyme abnormalities have been found in ~10-40% of SS patients and may be caused by drug toxicity, primary biliary cholongitis, chronic active autoimmune hepatitis (AIH) and sclerosing cholangitis (SC) [102,147–150]. Although considered an exclusionary diagnosis in the last 3 classification criteria sets for SS, chronic hepatitis C infection (HCV) should always be tested in any patient with sicca symptoms and abnormal liver function tests. Hepatitis C is highly prevalent among "baby boomers" in the United States [151] and certain European populations [152] and, can cause a clinical syndrome that closely resembles SS [153] Diagnosis of the HCV-associated sicca syndrome requires demonstration of viral persistence in blood or saliva by polymerase chain reaction or documentation of chronic liver disease consistent with HCV in a patient with negative anti-SSA/SSB.

Primary biliary cholangitis (PBC) is an autoimmune disease of the bile ducts leading to bile duct destruction, cholestasis, and liver failure [154]. There is a female to male ratio of 9:1 with a prevalence that various by geography and an onset typically between 40 and 60 years of age [155]. Patients with PBC often present with fatigue and pruritus yet ~50-60% are asymptomatic at diagnosis [156]. It is interesting to note that subjective and objective evidence of dry eyes and dry mouth are frequently noted (~30-70%) in PBC patients [102,157]. PBC has been reported in ~2% of pSS patients in a large registry of 866 pSS patients [68] and in ~4-5% in smaller studies [62,150,158]. Among those with PBC, SS is common. The prevalence of SS has been reported as 36% in one study of 322 PBC patients and as 10% in another of 1032 PBC patients [102,159,160]. Diagnosis of PBC is can be made with elevated levels of alkaline phosphatase (> 2x the upper limit of normal) or GGT (> 5x the upper limit of normal), anti-mitochondrial antibody (AMA) testing, and/or chronic granulomatous cholangitis on liver biopsy [155]. AMA (with an M2 pattern) testing is highly sensitive (95%) and highly specific (98%) for the diagnosis [154,155] and is usually positive years before the diagnosis of PBC is made [155]. Positive AMA testing has been reported in ~2-8% of SS patients, 1/2 of whom had no clinical or laboratory evidence of liver disease [102,161]. With the high sensitivity and specificity of the AMA test, it is not surprising that in studies of non-SS patients with no overt evidence of liver disease, those with positive AMAs still had a high risk of going on to develop symptomatic PBC [161]. Given the fact that AMA testing is highly accurate for a disease that is frequently asymptomatic at presentation and can progress to liver failure, some authors have recommended routine AMA testing in SS patients, even in the absence of evidence of overt liver disease [102,162]. These authors note that early use of ursodeoxycholic acid (UDCA) in such patients could potentially prevent progression to cirrhosis [162,163]. The prognosis of PBC is generally good with only a minority of those treated with UDCA evolving to cirrhosis and 2 out of 3 PBC patients treated with UDCA have a nearly normal life expectancy [155].

Autoimmune hepatitis (AIH) is a chronic disease characterized by autoimmune destruction of hepatocytes, increased serum autoantibodies, increased serum aminotransferases, increased gamma-globulin levels, as well as typical but non-specific findings on liver biopsy [155]. There is a female to male ratio of 4:1 and an incidence estimated at 1 per 100,000 person-years [155]. The onset usually occurs prior to 45 years of age and is typically insidious [155]. Signs and symptoms may include fatigue, anorexia, jaundice, hepatosplenomegaly, rash, and arthralgia [155]. There are two types of AIH, type I and type II [155]. Type I is associated with ANA and/or anti-smooth-muscle antibodies (anti-SM) (found in up to 80% of cases) [155]. Type II is associated with anti-liver kidney microsomal type I antibodies (anti-LKM) [155]. Other autoantibodies that can be associated with AIH include anti-LC1 (correlates w/ more severe disease), p-ANCA, anti-SLA/LP (10-30%), anti-asialoglycoprotein receptor antibodies (correlates w/ more severe disease) [155]. Less specific autoantibodies found in AIH include anti-cardiolipin (40%), anti-chromatin, anti-dsDNA (up to 34%), RF, anti-histones (up to 35%), SSA, and CCP (9%). The diagnosis of AIH can often be established on clinical grounds though liver biopsy may be necessary [155]. Among patients with AIH, SS has been reported in up to 7% [155]. AIH is a rare manifestation of SS, having been reported in about 1% of pSS in a large registry of 866 pSS patients and in up to 4% in other studies [68,102]. All of these have been type I AIH. Type II AIH has not been reported in patients with pSS [161]. About 10% of AIH patients also have a positive AMA and are felt to have an AIH/PBC overlap syndrome [161]. In one study looking at patients with an AIH/PBC overlap, SS was reported in 8%, more than any other systemic autoimmune disease [161]. Although AIH can progress to cirrhosis and even hepatocellular carcinoma (HCC), when properly treated, few develop cirrhosis at follow-up and the 10-year survival rate is greater than 90% [155]. Treatment typically consists of prednisone with or without azathioprine [155].

Sclerosing cholangitis (SC) is a liver disease characterized by progressive inflammation and fibrosis of the intra- and extra-hepatic bile ducts leading to significant morbidity and mortality [155,161]. It is rare with a prevalence of 10 per 100,000 in the United States and may present with abdominal pain, nausea, and jaundice [155,161]. Though it can be found in 7% of IBD patients, SC is scarcely found in SS with only 13 cases noted in the literature [155,161]. Interestingly, 12 of the 13 SS/SC cases also had chronic pancreatitis. Despite treatment with medications and endoscopic interventions, the median time to liver-transplant or death in SC patients is 18 years [155].

2.3.18. Renal manifestations

Clinically overt renal disease is unusual in SS, reported in about 5% of patients in large retrospective studies [66,83,88]. However, the most common renal manifestations, tubulointerstitial nephritis and renal tubular acidosis, are often subtle and insidious, frequently presenting asymptomatically and with seemingly insignificant laboratory abnormalities [164,165]. When specifically looking for these manifestations in prospective studies, the prevalence of renal disease in SS has been shown to be as high as 50% [166]. More dramatic renal presentations such as acute glomerulonephritis is noted in a minority of cases. The onset of clinically significant renal disease in SS seems to occur around the time of SS diagnosis or shortly thereafter though ~10% may occur 5 or more years later [167]. Overall, among those with renal involvement, the loss of renal function tends to be mild with only ~5-10% progressing to end-stage kidney disease [167]. Active vigilance for renal manifestations of SS is crucial as early diagnosis can potentially help prevent renal failure and other sequelae.

2.3.19. Tubulointerstitial nephritis

Though many may equate glomerulonephritis with autoimmune disease, the most common renal lesion found in those with SS is tubulointerstitial nephritis (TIN). One large retrospective French study of 95 SS patients with biopsy-proven renal involvement found TIN in 98% of the biopsies, ~75% of which occurred in isolation without glomerulonephritis ("isolated" TIN) [167]. Smaller studies looking specifically at renal biopsies note TIN in ~50-80% of biopsy samples [88,164,166,168].

TIN in SS typically presents and progresses insidiously with minimal symptoms if any at all [165]. This is why, without specifically screening for it, it is under-diagnosed and reported as infrequent in large retrospective cohorts [165,167]. Clues for TIN in SS may include electrolyte disturbances, elevations in serum creatinine, and low range proteinuria [165]. The rise in creatinine is often subtle and acute kidney injury is uncommon [165]. The low molecular weight proteinuria (tubular proteinuria) found in TIN can be missed since it is not detected on urine dipstick testing [165]. Hypertension tends to occur late in the disease course [165].

The pathophysiology of TIN consists of inflammation of the interstitium which causes tissue fibrosis and atrophy that ultimately leads to

chronic kidney disease and, in many cases, renal tubular acidosis [165,169]. Auto-antibodies, such as those against the carbonic anhydrase of the intercalated cells, have been found but it is not clear if these are a cause or an effect of TIN [165]. The inflammatory infiltrate of TIN is made mostly of T-cells, B-cells and plasma cells [165,167]. The T-cells predominate and are mostly CD4+ [167,170]. This overall pattern is similar to that found in minor salivary gland infiltration in SS [165,167]. The pattern and degree of infiltration in TIN is highly variable. It can be diffuse or patchy [165,169]. It can be light, involving < 25% of the interstitium, to heavy, involving > 75% of the interstitium [167,169]. Permanent damage, in the form of fibrosis and atrophy, is often found [165]. The Jasiek, et al. study noted that over 25% of the cortex was fibrosed in about 2/3 of the biopsies and that this is a strong marker for poor renal prognosis [167]. It is important to note that the histology of TIN in SS is nonspecific and therefore it is important to consider the differential diagnosis for TIN when encountered [165]. The differential diagnosis for TIN includes IgG4 related disease (look for increased staining for IgG4+ plasma cells & storiform fibrosis), sarcoidosis (look for granulomas), infections such as pyelonephritis, tuberculosis, leptospirosis, hantavirus infection, and the use of drugs such as NSAIDs, beta-lactam antibiotics, allopurinol, the tubulointerstitial nephritis and uveitis syndrome (TINU), lymphoma, leukemia, and the use of Chinese herbs [165].

Case series of TIN in SS note a good response to glucocorticoids at doses > 0.5 mg/kg/d [165,166]. Though some series report improvement with concurrent immunosuppressive medication such as mycophenolate mofetil, there is no clear evidence that this strategy is superior to glucocorticoids alone [165]. In regards to the prognosis of TIN in SS, it seems there is a slow decline in renal function sometimes leading to end-stage kidney disease. One retrospective study reported that ~15% of SS patients with TIN required hemodialysis [88].

2.3.20. Distal renal tubular acidosis

Renal tubular acidosis is a condition in which the kidneys are unable to fulfill their function of maintaining proper acid-base balance in the body due to abnormalities of cells of the renal tubules resulting in metabolic acidosis. The most common cells involved in this process in SS are the alpha-intercalated cells of the collecting duct. The job of these cells is to secrete hydrogen ions into the urine to help keep the blood from becoming too acidic. In distal renal tubular acidosis (dRTA), due to a loss of the hydrogen ATPase enzyme, these cells fail to secrete adequate amounts of hydrogen ions in the urine and this results in a non-anion-gap metabolic acidosis [165]. To maintain electroneutrality, other cations are secreted instead such as potassium, calcium, and phosphorous. The loss of potassium can lead to severe hypokalemia that may interfere with muscle function and manifest as cramps and/or periodic paralysis [165]. The loss of calcium and phosphorous can lead to nephrolithiasis and/or nephrocalcinosis [170]. The mild metabolic acidosis can lead to bone loss and/or osteomalacia [166,171]. More recent prospective and cross-sectional studies specifically looking for renal abnormalities in SS patients show that dRTA occurs in ~10-40% of SS patients [166,171–173] and a retrospective study notes that dRTA was found in ~70% of SS patients with renal involvement [170,174]. Distal renal tubular acidosis can be the first and only renal abnormality in patients with SS and may present in a subtle fashion [165]. Mild hypokalemia, hyperchloremia, non-anion-gap metabolic acidosis, or a history of nephrolithiasis in a SS patient should tip one off to the possibility of an underlying dRTA [165]. Occasionally a so-called "incomplete" version of dRTA may exist in which there is no acidemia but the urine pH fails to decrease to < 5.3 after an ammonium chloride acid load [165]. dRTA in SS is usually associated with TIN [165]. Because of this, if dRTA is discovered in a SS patient, a renal biopsy should be strongly considered [165]. The treatment of dRTA is typically supportive including bicarbonate and potassium supplements along with close monitoring by a nephrologist [170].

2.3.21. Proximal renal tubular acidosis

When cells of the proximal tubule fail to properly reabsorb bicarbonate, metabolic acidosis can result in a process known as proximal renal tubular acidosis (pRTA). pRTA is rare, having been reported in 3% of SS patients with renal involvement [174]. In addition to bicarbonate, there may also be a failure to reabsorb phosphate, small proteins, amino acids, glucose and urate (a condition known as Fanconi syndrome) [170]. As with dRTA, pRTA in SS is often asymptomatic though it may result in osteomalacia, nephrolithiasis and nephrocalcinosis [165,170].

2.3.22. Diabetes insipidus

Nephrogenic diabetes insipidus is a condition in which the principal cells of the collecting duct are unable to properly concentrate urine leading to polyuria, nocturia, and polydipsia [170]. This is a fairly frequent finding occurring in 17-28% of SS patients according to prospective studies [164,170,172]. The management of diabetes insipidus is simply to drink enough water which is commonly done by SS patients anyway for symptoms of dry mouth and throat.

2.3.23. Glomerulonephritis

Unlike TIN which typically presents insidiously, glomerulonephritis (GN) in SS often presents in a dramatic fashion with hypertension, proteinuria, hematuria, and acute kidney injury [165]. The most common GN lesion found in SS is membranoproliferative glomerulonephritis which is typically due to immune complex deposition associated with cryoglobulinemia and low complement levels [88,165,167,170]. GN is not common in SS. According to two prospective SS cohorts, the prevalence of GN was found to be only ~2% [62,172]. Of renal biopsy samples, Jasiek et al. noted glomerular lesions in 23.2%, mostly with concurrent TIN [167]. Studies with far fewer samples have shown a GN frequency of 8% to 48% [88,164,168]. GN presents later in the disease course than TIN [88] [69,152]. Treatment is typically with high-dose glucocorticoids and other immunosuppressive medications like mycophenolate mofetil, rituximab, and cyclophosphamide [165]. GN in SS has been associated with NHL and increased mortality [88,165,170].

2.3.24. Pulmonary manifestations

Clinically significant pulmonary involvement occurs in 10-20% of SS patients and is a significant cause of disease-related mortality [62,66,69,83,175–178]. The most common pulmonary manifestations are airway disease, interstitial lung disease (ILD), and xerotrachea [175,176,178,179]. The most common respiratory symptoms in SS are cough and dyspnea though some with abnormal objective pulmonary findings are asymptomatic [177,178] [159,160].

2.3.25. Respiratory infections

Recurrent respiratory tract infections such as sinusitis and bronchitis are not uncommon in SS with pneumonia reported in 10-35% [176]. Potential contributors to recurrent respiratory tract infections may include decreased mucociliary clearance, gastroesophageal reflux, bronchiectasis and immunosuppression [176].

2.3.26. Cough

Chronic cough is reported in up to 60% of SS patients and may affect quality of life [176]. One study noted that cough in SS was productive in about half of cases and dry in the other half [175]. Potential causes of cough in SS include xerotrachea, airway hyperresponsiveness, bronchiectasis, gastroesophageal reflux, and ILD [176].

2.3.27. Pulmonary testing

Given the morbidity associated with the pulmonary manifestations of SS routine screening is recommended for every patient with chronic respiratory symptoms. Evaluation for lung disease in SS may include pulmonary function testing (PFT), high-resolution computed tomography (HRCT) scanning, and lung biopsy. The diagnostic yield of these

studies was described in a systematic literature review that noted pulmonary involvement in 795 (16%) of 4897 SS patients diagnosed by AECG criteria [178].

Among 330 patients tested PFT results were abnormal in 64%. A restrictive pattern was noted in ~65% and an obstructive pattern in ~20%.

HRCT findings were described in 526 patients. The most common CT findings were bronchiectasis/bronchiolitis (50%) and ground-glass opacities (50%). Less frequent findings included: pulmonary nodules (23%), interlobular septal thickening (23%), reticular opacities (22%), cysts/bullae (22%), airspace opacities (14%), honeycombing (13%), non-septal linear/plate-like opacities (12%), mosaic perfusion/attenuation (7%), tree-in-bud opacities (6%), emphysema/air trapping (5%), and pleural thickening/effusions (5%).

Of the 146 SS patients who underwent lung biopsy the most common histopathologic findings included: non-specific interstitial pneumonia (NSIP) in 45% followed by bronchiolitis in 25%, usual interstitial pneumonia (UIP) in 16%, lymphocytic interstitial pneumonia (LIP) in 15%, and organizing pneumonia (OP) in 7%. Less common findings included amyloidosis (6%), pulmonary lymphoma (4%), and non-caseating granulomas (3%).

2.3.28. Interstitial lung disease

Interstitial lung disease (ILD) has been reported in 3-11% of SS patients and is a significant cause of mortality [176,177]. Most patients present with dyspnea and cough. A restrictive pattern is typically noted on PFTs with a diminished diffusing capacity of carbon monoxide [176]. One recent French series of 264 consecutive SS patients with a mean follow-up of 24 months noted ILD in 8% (21/263) [177]. Similar to the findings mentioned in the large systematic review noted above, the most common ILD patterns were NSIP in ~30%, followed by UIP in ~25%, LIP in ~10%, OP in ~10%, and non-specific findings in the rest. The onset of ILD preceded SS diagnosis in ~25%, was concurrent in ~25%, and followed the diagnosis in ~50%. Clinical presentations were varied and acute/subacute in ~50%, insidious in ~25%, and asymptomatic or subclinical in ~25%. The disease courses of the 21 patients after follow-up demonstrated improvement in ~15%, stabilization in ~50%, and deterioration in ~35%. Factors at the time of SS diagnosis that predicted the development of ILD included older age (63 vs 55 years, $p = 0.044$), Raynaud's phenomenon (57.1% vs 22.2%, $p = 0.001$), and esophageal involvement (23.8% vs 2.7%, $p = 0.001$). Factors associated with a deteriorating course included older age ($p = 0.038$) and esophageal involvement ($p = 0.038$).

2.3.28.1. NSIP. NSIP is the most common subtype of ILD in SS [176]. The histopathology consists of interstitial inflammation and fibrosis with a uniform appearance and relative preservation of the lung architecture [176]. The HRCT pattern is typically bibasilar and symmetric with reticular changes, traction bronchiectasis, and ground glass opacities. [176]. The response to treatment is variable but most patients demonstrate improvement or stabilization of their lung disease with a 5-year survival rate of 83% [176].

2.3.28.2. UIP. UIP is the next most common subtype of ILD in SS and the HRCT pattern is characterized by reticular changes, bronchiectasis, and honeycombing that is patchy and predominates at the bases and periphery [176]. Histopathology reveals honeycombing, minimal interstitial inflammation and patches of interstitial fibrosis intermixed with normal parenchyma [176]. UIP is difficult to treat and has a worse prognosis than NSIP [176].

2.3.28.3. LIP. Histopathology of LIP consists of diffuse polyclonal lymphocytic interstitial infiltrate with lymphoid follicles and germinal centers [176]. Follicular bronchiolitis is often associated with LIP. The HRCT pattern typical of LIP consists of nodules, ground-glass opacities, thickening of the interlobular septa, and cysts in ~60-80% [176]. Most SS patients with LIP stabilize or improve with glucocorticoid therapy [176]. Lung biopsy should always be performed in patients with consolidating nodules, mass-like opacities, mediastinal adenopathy or treatment refractory cases to rule out lymphoma [176].

2.3.28.4. OP. The HRCT pattern typical of OP consists of multiple areas of consolidation in the periphery sometimes with ground glass opacities and centrilobular nodules [176]. In doubtful cases a biopsy is required to confirm this diagnosis. The pathology will show polypoid intraluminal masses of fibroblasts, myofibroblasts and collagen within the alveolar ducts and spaces surrounded by alveoli and bronchioles with coexistent chronic inflammation.

2.3.29. Airway disease

Manifested mainly by cough, airway involvement in SS is due to dryness from exocrine gland dysfunction and/or lymphocytic infiltration of the trachea, bronchi, and/or bronchioles [176]. Bronchial hyperresponsiveness to environmental stimuli is noted in up to 60% of SS patients [176]. CT findings related to airway disease include bronchiectasis, bronchiolectasis, airway wall thickening, centrilobular nodules, tree-in-bud opacities, mosaic attenuation, air trapping, and subsegmental atelectasis [175,176]. Airway disease typically has minimal effect on respiratory function and, therefore, is not a significant contributor to mortality in SS patients [176].

2.3.30. Uncommon pulmonary manifestations

Pleurisy and pleural effusions may occur in SS albeit rarely [180–183]. The effusion can be unilateral or bilateral and is usually exudative with a lymphocytic predominance.

Pulmonary hypertension documented by cardiac catherization has also been described in SS and causes morbidity and mortality similar to that seen in other connective tissue disorders [184,185].

2.3.31. Dermatologic manifestations

Sjögren's syndrome commonly affects the skin and dermatologic manifestations of SS often precede sicca symptoms of dry eye and dry mouth [186]. The most frequent is xerosis (dry skin), occurring in about 50%. Other relatively common skin manifestations include Raynaud's phenomenon (~15-30%), cutaneous vasculitis (~10%), and annular erythema (~10%) [62,66,68,69,186].

Raynaud's phenomenon (RP) is a clinical diagnosis that typically manifests as sudden-onset well-demarcated color changes of the distal digits that last up to 30 minutes or so and then resolve. The classic pattern of color change is white to purple/blue then red though this pattern is noted in a minority of patients. Though RP can lead to distal digital ulceration from repeated episodes of ischemia, this is rarely noted in SS and more typically found in systemic sclerosis. As such, discovery of digital ulcers in a SS patient with RP should prompt an evaluation for concurrent systemic sclerosis [186].

Cutaneous vasculitis in SS can manifest as purpura, maculopapular rash, urticaria, and cutaneous ulcers [186]. The location of these findings is typically on the lower extremities [186]. Pathologically, the most common finding is leukocytoclastic vasculitis followed by cryoglobulinemic and urticarial vasculitides [186]. Overall, cutaneous vasculitis in SS is associated with more systemic manifestations, more severe disease, lymphoma and poor prognosis [186]. In one study of 515 SS patients followed for a mean of 110 months, those with cryoglobulinemic vasculitis had a higher risk of death compared to those without cryoglobulins (HR 4.36, 95% CI: 1.32, 14.47) [187].

Annular erythema (AE) in SS resembles subcutaneous lupus erythematosus (SCLE) and, as suggested by its name, appears as polycyclic erythema. AE in SS and SCLE can be difficult to tell apart as they essentially appear the same morphologically and are both associated with SSA positivity [186]. AE in SS is associated with less severe systemic disease and better overall prognosis [186].

Amyloidosis is rarely found in SS but when it is, it is typically

localized to the skin and/or lungs [186]. Localized cutaneous amyloidosis (LCNA) appears as a single nodule, sometimes multiple nodules, mostly on the legs, arms, trunk and face [186]. Although LCNA is rare, 25% of reported cases have been associated with SS [186].

Less common dermatologic manifestations noted in SS include pruritis, vitiligo, alopecia, anetoderma, Sweet syndrome, lichen planus, granulomatous panniculitis, sub corneal pustular dermatosis, erythema elevatum diutinum, erythema multiforme-like, erythema perstans-like, and erythema nodosum-like lesions [186].

2.3.32. Neurologic manifestations

The prevalence of neurologic disease in SS is ~20% and the peripheral nervous system is more frequently affected than the central nervous system. Neurological symptoms, however, including headaches, cognitive dysfunction and affective disorders have been observed in as many as ~70% [188–190]. The onset of neurologic disease in SS frequently predates the diagnosis of SS and often occurs in the absence of sicca symptoms [188,191]. Not surprisingly, this may delay treatment until the diagnosis of SS is established. Typically, neurologic manifestations in SS patients are mild and treatment is supportive. However, occasionally, cases are progressive and/or debilitating and warrant consideration of immunomodulating/immunosuppressive therapy.

2.3.33. Peripheral nervous system involvement

Peripheral nervous system (PNS) manifestations in SS include axonal sensory/sensorimotor polyneuropathies, small fiber sensory neuropathy, sensory ataxic neuronopathy (also known as sensory ganglionopathy), cranial nerve neuropathies, radiculoneuropathy, autonomic neuropathies, chronic inflammatory demyelinating polyneuropathy and mononeuritis multiplex [188,189]. The most common patterns are axonal sensory polyneuropathies and small fiber sensory neuropathies [188,189]. More than one neuropathy type may coexist in any given patient [192].

Distal axonal sensory polyneuropathy affects large nerve fibers and is the most common PNS manifestation of SS [189]. It typically presents with indolent, mild paresthesias of the distal lower extremities and, the upper extremities are involved in about 20% of cases [189]. On exam, there are sensory deficits to light touch, proprioception and vibration of the affected extremity in a "stocking-glove" distribution and diminished or absent deep tendon reflexes. Electrodiagnostic studies are frequently abnormal. Sensorimotor polyneuropathy occurs when there is concurrent weakness. The weakness is generally mild and affects the toe/foot extensors [188,189].

Small fiber neuropathy occurs when there is damage to the A-δ small myelinated fibers and/or unmyelinated C fibers that conduct signals of pain and temperature and leads to burning paresthesias and shooting pain often with allodynia and hyperalgesia [193]. It is estimated to affect 5-10% of SS patients [189]. Symptoms can be symmetric and affect mainly the distal extremities or they can be patchy [188]. The onset of symptoms is typically subacute or chronic [189]. On exam, there is a loss of pinprick and temperature sensation but no deficit in strength, light touch sensation, proprioception, or deep tendon reflexes [188]. Nerve conduction studies are characteristically normal; diagnosis is made by skin biopsy demonstrating a decrease in intraepidermal nerve fiber density [193].

Sensory ataxic neuronopathy, also known as ganglionopathy, is a rare and often dramatic type of neuropathy found in SS [194]. Damage to the dorsal root ganglia from lymphocytic infiltration (ganglionitis) leads to a marked loss of proprioception, sensory ataxia and difficulty with fine motor skills [189]. Patients often present with gait instability that eventually requires the use of a wheelchair to prevent falls. Deep tendon reflexes are diminished or absent and vibration sensation is abnormal with preservation of motor function. Nerve conduction studies demonstrate decreased sensory nerve action potentials and MRI may show increased hyperintensity of T2 weighted images in the posterior columns [188,189].

Mononeuritis multiplex is a painful condition in which damage to two or more nerves occurs in succession in an acute/subacute fashion leading to sensory and motor deficits [195,196]. It can present as foot drop or wrist drop with patchy sensory loss or as an asymmetric peripheral neuropathy. Symptoms usually begin in lower limbs and affect the tibial or peroneal divisions of the sciatic nerve. Inflammation of epineural and perineural blood vessels that perfuse the involved nerves leads to infarction. Electrodiagnostic studies demonstrate an asymmetric peripheral neuropathy involving 2 or more sensory or motor nerves. A sural nerve or superficial peroneal nerve biopsy or simultaneous nerve-muscle biopsy will show definite vasculitis in up to 77% of cases [197]. This vasculitis often affects other organs at the same time and causes constitutional symptoms. Mononeuritis multiplex in SS has a strong association with serum cryoglobulinemia [188]. The prevalence of mononeuritis multiplex in SS is noted to be 12% in some studies [189]. Mononeuritis multiplex is a very serious manifestation that requires expeditious evaluation and treatment with immunosuppressive therapy.

2.3.34. Cranial neuropathy

In two large cohorts of SS patients with neurological disease the prevalence of peripheral cranial neuropathies ranged from 16-20% [191,192]. Pure sensory trigeminal neuralgia is frequently described in most series and typically affects the maxillary branch of the trigeminal nerve in a unilateral distribution [189]. The major symptom is lancinating or searing facial pain that last seconds to minutes and can occur spontaneously or be triggered by touching the face, chewing, speaking or brushing the teeth. Other common symptoms related to cranial neuropathies include hearing loss and vestibular symptoms (cochlear nerve), recurrent diplopia (CN III, VI) and Bell's palsy (CN VII). Multiple cranial neuropathies in the same patient have also been described [192].

2.3.35. Central nervous system involvement

Central nervous system (CNS) involvement in SS varies greatly in significance ranging from mild cognitive dysfunction to transverse myelitis and resultant paralysis [188,189]. Other manifestations include aseptic meningitis, seizures, headaches, optic neuritis, disseminated encephalopathy, and multiple-sclerosis-like demyelinating lesions [189–191,198,199].

Demyelinating CNS lesions can occur in the white matter of the brain and spinal cord of patients with SS and mimic the relapsing-remitting and primary progressive forms of multiple sclerosis (MS). This can cause various symptoms including visual loss (optic neuritis), paresis of limbs, ataxia, sphincter dysfunction, cognitive dysfunction and sensory symptoms [189]. Features that help distinguish SS from MS may include a lack of oligoclonal bands (OCB) on cerebral spinal fluid analysis (OCB are noted in 95% of MS and only 30% of SS), the presence of longitudinally extensive transverse myelitis on MRI (common in SS-related transverse myelitis and highly atypical in MS), and the white matter lesions demonstrated on brain MRI in SS that, unlike in MS, do not enhance and tend to spare the corpus callosum [188]. The presence of extra glandular manifestations such as arthritis and interstitial lung disease also help confirm a suspected diagnosis of SS.

It must be kept in mind, however, that non-specific white matter lesions are not infrequently found on brain MRI of SS patients and sometimes related to other causes. Without corresponding neurologic signs or symptoms, these are often not clinically significant and probably reflect microvascular ischemic changes related to cardiovascular risk factors and not autoimmunity [188].

Like other autoimmune disorders SS has also been associated with neuromyelitis optica (NMO) or Devic syndrome [51,200,201]. NMO is an autoimmune disease characterized by optic neuritis, longitudinally extensive transverse myelitis (spanning more than 2 vertebral segments) and anti-aquaporin-4 (NMO-IgG) antibodies. More recently, the

term "NMO spectrum disorder" (NMOSD) has been used to describe a wider range of NMO positive neurologic conditions that share some features of NMO but don't meet the criteria for the diagnosis of this disorder [201,202]. Given the fact that aquaporin-4 antibodies were only described in 2004, it is conceivable that some of the past cases of SS described as MS mimics may actually be attributed to NMO or NMOSD.

2.3.36. Autonomic nervous system involvement

Autonomic nervous system dysfunction (dysautonomia) in SS can manifest as persistent tachycardia, orthostatic hypotension, GI dysmotility, bladder dysfunction, and hypohydrosis/anhidrosis [122,189,192]. The prevalence of dysautonomia is highly variable, reported in 3-50% of SS depending on how it was defined and assessed [189]. Potential etiologies include cholinergic neurotransmission blockade by cytokines or autoantibodies, T-cell infiltration, and autonomic nerve destruction [189].

2.3.37. Cognitive dysfunction

Neuropsychological impairment a.k.a. "brain fog" is a common complaint among SS sufferers and characterized by difficulty with short term memory, focus, concentration and mental clarity. The pathogenesis is poorly understood. It may be idiopathic or related to one or more secondary causes including anxiety/depression, chronic pain, non-restorative sleep, vitamin deficiencies, hypothyroidism or medication side effects. The self-reported prevalence in a recent survey of SS patients was 53% [203]. Cognitive dysfunction can occasionally be the presenting manifestation of the disease [204]. Neuropsychological testing is the most helpful means to characterize the nature and degree of impairment in patients with persistent or disabling symptoms. Interestingly, discrepancies sometimes exist between patient reported complaints of memory loss and the findings of objective tests [191,205].

The results of neuropsychological testing vary among different SS patient groups and have proven difficult to interpret across studies. This may relate to various factors including small sample size, lack of uniform diagnostic criteria, different instruments used and varying efforts to control for confounding variables that could potentially influence study results such as age, medication use, depression, poor sleep and chronic pain. The most frequent abnormalities reported to date include: deficits with verbal memory, verbal processing, language skills, attention, concentration and executive functioning [205–215]. Magnetic resonance imaging of the brain in SS patients with cognitive dysfunction can be normal or reveal findings of cerebral atrophy or white matter changes [208,216–219].

Frank dementia is uncommon in SS but has occasionally been reported [204]. Therefore, any individual who presents with severe and/or progressive cognitive dysfunction, especially when associated with other neurological signs and symptoms should be evaluated for central nervous system Sjögren's. One study also reported that patients who score multiple domains below the fifth percentile on neuropsychological testing are also at high risk for this complication [204].

2.4. Conclusions

In summary, Sjögren's syndrome can cause a myriad of signs and symptoms that can affect virtually any organ system. The clinical manifestations may arise from multiple mechanisms including exocrine gland dysfunction, lymphocytic infiltration of other organs, associated autoimmune diseases, immune dysregulation and other coincidental comorbidities such as fibromyalgia. A comprehensive treatment plan necessitates an understanding of the entire spectrum of disease especially, common SS-related problems. A complete history and physical examination including periodic clinical and laboratory re-assessment for internal organ involvement, lymphomas and other complications should help clinicians identify pertinent patient problems earlier in the course and initiate treatment before irreversible organ damage and/or serous morbidity occur. The challenge of diagnosing SS is further discussed in the next section.

3. Challenge of diagnosis

Estimates on the prevalence of Sjögren's syndrome in various populations differ widely [220–223]. With a recent estimated prevalence between 2.2 and 10.3 cases per 10,000 in the U.S. [224], primary Sjögren's Syndrome should no longer be designated as a rare disorder (i.e. affecting < 200,000 people) according to the U.S. Rare Diseases Act of 2002[1]. Despite this observation, Sjögren's continues to present a common diagnostic challenge for practicing clinicians. The average lag between symptom onset and diagnosis is reported by the Sjögren's Syndrome Foundation to be 2.8 years[2].

The challenge of diagnosing Sjögren's is multifaceted, and may involve both patient and provider factors. Onset of symptoms is often insidious and non-specific and, there are currently no universally accepted diagnostic criteria. Providers unfamiliar with the wide spectrum of extra-glandular presentations and associated conditions may not consider Sjögren's syndrome as a potential diagnosis in an individual without dry eyes or dry mouth. However, sicca symptoms are not always present at the time of diagnosis. This scenario is particularly common among individuals who present with a neurological manifestation of the disease [191]. Moreover, recent data have shown significant rates of under-referral to relevant subspecialists even if the patient presents with typical sicca symptoms [225]. Even when characteristic glandular and extra-glandular symptoms are absent, SS can still occasionally be present. Further evaluation should also be considered if incidental imaging findings suggest the diagnosis. This last scenario may be particularly problematic due to the fact that imaging in SS has been a relatively under-represented topic in the rheumatology literature.

3.1. Importance of correct diagnosis

The ability to correctly diagnose Sjögren's syndrome is a skill that has important implications regarding patients' quality of life, as well as the overall morbidity associated with the disease. Although no large randomized controlled trials to date have identified a pharmacologic intervention that effectively alters the course of the disease, symptomatic management and monitoring tools are available that should be offered to every patient diagnosed with SS. Clinical practice guidelines are now available to guide this process [226–234].

3.1.1. Health-related quality of life

The negative impact of primary Sjögren's syndrome on patients' perceived health-related quality of life has well been documented [235,236]. Based on conclusions from a recent large therapeutic trial, patient-reported intensity of global dryness, pain and fatigue were stronger predictors of patients' poor quality of life than systemic activity as measured by a physician [237]. This observation provides an easily identifiable treatment opportunity for clinicians [226].

Notably, the above study used two validated tools, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), to objectively measure patient-reported outcomes and systemic disease activity, respectively [238]. Although developed as outcome measures for research, these scoring instruments could also potentially be used in clinical practice for therapeutic monitoring of patients with established SS.

[1] Rare Diseases Act of 2002, Public Law 107-280 – November 6, 2002.
[2] www.sjogren's.org. January 27, 2019.

3.1.2. Associated autoimmune diseases, hematologic and lymphoproliferative disorders

Additional examples that emphasize the importance of a timely and correct diagnosis in SS include the serious morbidity that may result from associated autoimmune disorders and the occurrence of life threatening extra-glandular manifestations such as interstitial lung disease or lymphomas.

Statistics from long-term outcome studies suggest that up to 71% of patients with primary SS develop at least one of the above problems during the disease course. Autoimmune thyroid disease is most frequently observed among the autoimmune diseases associated with SS but celiac disease, primary biliary cirrhosis, chronic active autoimmune hepatitis, myasthenia gravis and pernicious anemia also occur. Extra-glandular manifestations and/or associated autoimmune conditions are most frequently observed among females as well as those with anti-SSA/ SSB antibody positivity, cryoglobulins and hematologic abnormalities [239,240].

Hematologic abnormalities are a common finding in patients with primary Sjögren's Syndrome and may include hypergammaglobulinemia (37%), monoclonal gammopathy of undetermined significance (MGUS) (10%) or hypogammaglobulinemia (5%) [239]. Patients with MGUS must be closely monitored for the development of multiple myeloma and/or lymphomas, and individuals with hypogammaglobulinemia may develop recurrent infections during the course of the disease [241]. Significant hematologic abnormalities often occur relatively late in the disease and are also associated with the presence of anti-SSA/SSB [239].

The most important hematologic complication of primary Sjögren's syndrome is the development of non-Hodgkin's B-cell lymphomas which affect 5-10% of patients and typically occurs 10-15 years following diagnosis [239,242]. In some patients this may be explained by the overexpression of B-cell activating factor (BAFF) and a mutation in the tumor suppressor gene, TNFAIP3 a.k.a A20 that results in uncontrolled B cell proliferation and survival [243,244].The most common type of lymphoma affecting Sjögren's patients is a low-grade marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type, followed by diffuse large B-cell lymphoma. Lymphomas typically present in the parotid glands, but can also affect the submandibular glands, as well as extra-nodal sites including MALT lymphomas of the stomach, lungs, liver, spleen and orbit [245]. Among the major salivary glands, predilection for the parotid gland is likely attributable to its unique feature of having embedded lymphoid tissue within the parenchyma of the gland, a result of late parotid encapsulation in embryonic development [246]. A significantly increased incidence of non-Hodgkin's B-cell lymphoma has been observed among men with SS as well as patients with cutaneous vasculitis, persistent salivary glandular swelling, low serum complement C4 levels and mixed monoclonal cryoglobulinemia [239,247]. More recently, the list of risk factors for lymphoma has further expanded to include CD4 lymphopenia, rheumatoid factor positivity, lymphadenopathy, splenomegaly, an ESSDAI score ≥ 5, a salivary gland biopsy showing a focus score $\geq$ 3/ 4 mm^2 or the presence of ectopic germinal centers within the biopsy [248].

3.2. Clinical presentation

The spectrum of clinical presentations among patients with primary Sjögren's ranges from sicca syndrome (derived from the Latin *siccus*, meaning dry) to systemic (extra-glandular) involvement. Interestingly, sicca symptoms may be minimal or absent in this latter group at the time of initial presentation. Additionally, patients who undergo further evaluation for abnormal serologies (e.g. antinuclear antibody, rheumatoid factor positivity), often drawn because of vague symptoms, will sometimes have SS as the final diagnosis. Finally, Sjögren's is occasionally suspected when imaging abnormalities of the major salivary glands are discovered serendipitously during evaluation for other problems (e.g. CT or MRI for neck mass). The proportion of individuals presenting with some form of sicca syndrome is estimated at 80-85% [231,245]. A list of signs and symptoms suggestive of dryness observed in primary Sjögren's is provided in Table 1 [231]. The prevalence of extra-glandular manifestations as the initial presentation of SS from a review by the EULAR-SS Task Force in 2016 is summarized in Table 2 [231].

Table 1
Sicca signs and symptoms in primary Sjögren's syndrome.[a]

Signs and symptoms of dryness
Ocular
• Bacterial keratitis
• Blepharitis
• Conjunctivitis
• Corneal ulceration
• Corneal vascularization and opacification
• Decreased visual acuity
• Eye fatigue
• Erythema
• Photosensitivity
Oral
• Adherence of food to the mucosa
• Angular cheilitis
• Candida infection
• Difficulties in speaking or eating
• Difficulty with dentures
• Disappearance of the usual pooling of saliva in the floor of the mouth
• Dry and glazed oral mucosa
• Dysphagia
• Erythematous changes of the hard palate
• Fine wrinkles in the oral mucosa
• Local infection
• Partial or complete depapillation of the tongue
• Periodontal disease
• Red tongue with atrophic papillae
• Soreness
• Surface of the tongue red and lobulated
• Tooth decay
Other
• Chronic, nonproductive cough
• Cutaneous dryness
• Difficulty swallowing
• Dysphagia
• Dyspareunia
• Persistent hoarseness
• Pruritis in the outer ear and ear canal
• Vaginal pruritis

[a] Adopted from [231].

3.3. Classification criteria

In recent years, several useful sets of classification criteria have been developed to standardize the case definition of SS for patient enrollment in clinical trials and other research studies. Although not intended for diagnostic purposes, these criteria also provide a framework upon which further diagnostic testing for SS can be based. Today the most commonly recognized criteria are the 2002 American-European Consensus Group (AECG) criteria by Vitali et al. [249], the 2012 classification criteria of the Sjögren's International Collaborative Clinical Alliance (SICCA) by Shiboski et. al. [250] also known as the American College of Rheumatology (ACR)- SICCA criteria, and, more recently, the 2016 ACR-European League Against Rheumatism (EULAR) criteria (Table 3) [251].

Different criteria sets are still being utilized in different parts of the world and all have their respective advantages and disadvantages. All utilize the same definition of a positive labial minor salivary gland biopsy (i.e. focal lymphocytic sialadenitis with a focus score $\geq$ 1 /4 mm^2 tissue) but also permit classification as SS without performing a lip

Table 2
Extra-glandular/systemic presenting manifestations of Sjögren's.[a]

Organ-specific involvement	Definition	Prevalence (%)
Cutaneous		
	Clinical	77
• Annular erythema	Cutaneous ESSDAI	64
• Purpura/ ulcers	moderate/ high	75
• Raynaud phenomenon	Clinical	
Joints		
	Articular ESSDAI low	76
• Arthralgia	Articular ESSDAI	60
• Arthritis	moderate/ high	
Neurologic		
	Clinical/ EMG	46
• Axonal polyneuropathy	Clinical/ EMG	64
• Ganglionopathy	Clinical/ EMG	60
• Mononeuritis multiplex	Cerebral MRI	60
• MS-like disease	MRI	58
• Myelitis	EMG/ cutaneous biopsy	80
• Small fiber neuropathy		
Pulmonary		
	Pulmonary CT	22
• Interstitial lung disease	Ultrasound	55
• Pulmonary arterial hypertension		
Renal		
	Renal biopsy	28
• Glomerulonephritis	Clinical/ ultrasound/	25
• Interstitial cystitis	biopsy	

ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; EMG = electromyography
[a] Adopted from [231].

Table 3
2016 ACR-EULAR classification criteria for Sjögren's[1]

Inclusions

- anyone with dry eyes or dry mouth as defined by the 2002 criteria
- anyone with at least 1 extra-glandular manifestation as defined by the ESSDAI questionnaire

Test Item	Weight
+ lip biopsy (FS ≥ 1 / 4mm^2)	3
Anti-SSA (Ro) +	3
OSS[2] ≥ 5 (Van Bijsterfeld[3] ≥ 4)- 1 eye	1
Schirmer's (without topical anesthesia) ≤ 5mm/5 min.- 1 eye	1
Unstimulated whole mouth salivary flow ≤ 0.1 ml/ min	1

POSITIVE SCORE FOR SS ≥ 4

1. A positive biopsy is defined as focal lymphocytic sialadenitis with a focus score ≥1/ 4 mm^2 tissue surface area.
2. Ocular surface staining score (0-12 scale) for dry eyes using fluorescein/ lissamine green.
3. Van Bijsterveld score (0-9 scale) for dry eyes utilizing any vital dye

Exclusions: prior head & neck irradiation, active hepatitis C infection (confirmation by PCR), graft vs. host disease, acquired immune deficiency syndrome, sarcoidosis, amyloidosis, IgG4-related disease.

1. Adopted from [251].
2. Scale 0-12 [254].
3. Scale 0-9 [253].

biopsy if other parameters are satisfied. Additionally, all of the aforementioned criteria facilitate classification of SS based entirely on objective tests and endorse a case definition that does not absolutely require the presence of sicca symptoms; thus, the identification of SS is possible in patients who lack sicca symptoms. Differences arise, however, from varying opinions regarding the importance of including sicca symptoms in classification criteria for SS, recommendations for autoantibody testing and, testing for the evaluation of dry eyes and assessment of salivary gland involvement (Table 4). For example, salivary gland imaging was included in the 2002 model but omitted from more recent versions.

The 2002 criteria also allow the use of key symptoms for classification as SS and offer the largest menu of diagnostic tests from which to choose. These criteria also provide a case definition for both primary SS (i.e. SS that occurs without an associated connective tissue disease) and secondary SS (i.e. occurs in association with another connective tissue disorder e.g. rheumatoid arthritis). The 2012 criteria recommend classification based solely on results of objective tests, offer the greatest flexibility for autoantibody testing and advocate a more sensitive vital dye staining technique (combination fluorescein/lissamine green) to look for ocular surface damage.

The 2016 ACR-EULAR criteria represent a hybrid model of the two earlier versions and have been endorsed by both professional organizations to emphasize their importance. This version has a reported 87.4% sensitivity and 95.4% specificity for classifying primary Sjögren's Syndrome when compared to physician diagnosis as the reference standard [252]. Interestingly, the 2016 archetype only endorses the use of anti-SSA positivity as serologic proof of autoimmunity (see below). This model also offers the greatest flexibility for dry eye testing including use of 3 different vital dyes (rose bengal, fluorescein, lissamine green, or combination staining with fluorescein/lissamine green) and 2 different scoring systems [253,254] depending on which dye(s) are used. However, when the combination of fluorescein/lissamine green is utilized, the threshold for a positive result on a 0-12 scale (Ocular Surface Staining score) (OSS) was increased from ≥3 (recommended in 2012) to ≥ 5 (now recommended in 2016). An OSS of 5 using fluorescein/lissamine green also equates to a Van Bijsterveld score of ≥4 on a 0-9 scale (recommended in 2002) using a single vital dye such as rose bengal.

A further description of diagnostic testing for SS is outlined below.

3.4. Diagnostic evaluation

Unfortunately, at the present time, there are no diagnostic tests that have a high enough sensitivity and specificity to be used as stand-alone diagnostic studies in SS. Therefore, a comprehensive evaluation with assessment of multiple parameters is recommended.

3.4.1. Ocular assessment

Every patient with suspected SS should undergo a thorough examination by a cornea specialist or other eye care provider with expertise in this area. The evaluation of dry eyes should include an unanesthetized Schirmer's test to quantify tear production. A value ≥ 10 mm wetting of the testing strip/ 5 minutes is considered normal and a result ≤ 5 mm/5 minutes is highly suggestive of Sjögren's dry eyes. Another complementary test for dry eyes is ocular surface staining with vital dyes (i.e. rose bengal, fluorescein, lissamine green) to evaluate for corneal and/or conjunctival epithelial damage [253,254]. Since fluorescein typically reveals defects in the cornea but not the conjunctiva, combination staining with fluorescein and lissamine green (most sensitive way to document conjunctival abnormalities) has now become the procedure of choice for ocular surface assessment [254]. An Ocular Surface Staining Score (OSS) ≥3 and, later, ≥5 on a 0-12 scale was considered clinically significant as per the Whitcher scoring [254] system referenced in the 2012 and 2016 classification criteria, respectively. Rose bengal staining may be used as an alternate method to examine the eye surface but has recently fallen out of favor because it may aggravate stinging and burning sensations in patients with dry sensitive eyes. However, a Van Bijsterveld score ≥ 4 with rose bengal staining on a 0-9 scale [253] would satisfy the ocular component of both the 2002 and 2016 criteria. In addition to the above studies, inspection of the eyelids by slit lamp is recommended to look for signs of meibomian gland dysfunction which causes evaporative dry eye and further contributes to ocular discomfort.

Table 4
Comparison of classification criteria for Sjögren's.

	2002 AECG	2012 ACR-SICCA	2016 ACR-EULAR
Definition of positive biopsy	Focal lymphocytic sialadenitis FS ≥1/ 4 mm^2	Focal lymphocytic sialadenitis FS ≥1/ 4 mm^2	Focal lymphocytic sialadenitis FS ≥1/ 4 mm^2
Sialometry	Whole mouth salivary flow ≤ 0.1ml/min.	No	Whole mouth salivary flow ≤ 0.1ml/ min.
Inclusion of symptoms	Yes	No	No
Imaging	Salivary scintigraphy Sialography	No	No
Serologic proof of autoimmunity	Anti-SSA and/or SSB	Anti-SSA and/or SSB Or +RF(any titer) and +ANA ≥1:320	Anti-SSA
Dry eye tests	Schirmer's ≤ 5 mm/5 min. Or Single vital dye staining Van Bijsterveld ≥ 4	Combination vital dye staining **OSS ≥ 3**	Schirmer's ≤ 5 mm/5 min. Or Single vital dye staining Van Bijsterveld ≥ 4 Or Combination vital dye staining **OSS ≥ 5**
Required for classification as SS	3 objective tests Or 4 of 6 (objective tests and symptoms)	2 of 3 objective tests	≥4 of 9 points

3.4.2. Evaluation of salivary gland involvement

3.4.2.1. Sialometry. Salivary flow (sialometry) can be easily measured in the office by calculation of a whole mouth unstimulated salivary flow rate. This is accomplished by measuring a patient's salivary expectorant over 5-15 minutes, and dividing by the collection time. A score of ≤0.1mL/min meets inclusion for the 2016 ACR-EULAR Classification Criteria where expert opinion assigned it equal weight to a positive Ocular Staining Score and abnormal Schirmer's test [251]. It is also included in the 2002 AECG Classification Criteria along with abnormal scintigraphy and parotid sialography, as one of three diagnostic tests that can be used to demonstrate the salivary component of SS [249]. This contrasts sharply with the 2012 ACR-SICCA Criteria in which the only accepted proof of oral involvement was limited to a positive labial salivary gland biopsy in an attempt to improve criteria specificity [250].

Data have shown that the specificity of sialometry for Sjögren's syndrome is enhanced when combined with a positive lip biopsy [255] and/or with typical sialochemical changes [256], an analysis rarely done in a clinical setting. Higher sensitivity is also seen when sialometry of individual glands is performed rather than measurement of whole mouth salivary flow. For example, submandibular and sublingual involvement tend to occur before the parotids are affected in early Sjögren's [256]. Due to the need for specialized collection devices, however, sialometry of individual glands is never performed in routine rheumatology practice.

3.4.2.2. Scintigraphy. Salivary scintigraphy provides an alternate means to noninvasively assess major salivary gland function [257], and represents one of the few imaging modalities ever included in any classification criteria [249]. In the United States this procedure is more widely available than salivary gland ultrasonography and can be performed at any imaging facility with nuclear medicine capability. However, since the protocol is not yet standardized, the diagnostic and prognostic value of this study depends on the imaging techniques used and the center that performs it [257]. Therefore, cross comparisons of the sensitivity and specificity of scintigraphy vs. other imaging modalities (e.g. ultrasound) for the diagnosis of SS are currently uninterpretable. The protocol referenced in the 2002 American European Classification criteria measured isotope uptake into the major salivary glands (reflective of saliva formation) and spontaneous discharge in the resting state (i.e. between meals and overnight) [258]. Since that time, newer protocols have also incorporated the administration of a secretagogue into the procedure in order to measure stimulated function (i.e. after eating) [259,260].

A typical scan for a normal individual is represented in Fig. 1. The patient receives an intravenous injection of Tc-99m pertechnetate (150 μCi/Kg) and is scanned for 60 minutes in the anterior Water's view. Maximal isotope uptake by the major salivary glands occurs within the first 30 minutes and is followed by the spontaneous secretion of the isotope into the oral cavity through Stenson's and Wharton's ducts. A gustatory stimulus (lemon drops) is administered in the final 15 minutes of the procedure to examine stimulated function and, all of the activity in the major glands essentially drops out and appears in the oral cavity. Regions of interest can also be drawn around the parotids, submandibulars, oral cavity and scalp to generate background corrected time activity curves (not shown) to look for differences in function between the 4 visualized major salivary glands. In Sjögren's syndrome defects in all 3 phases of salivary gland function have been observed [260]. Thus, the procedure's ability to distinguish uptake failure from secretory failure may be a useful asset in guiding clinical management strategies and estimating outcomes.

3.4.2.3. Histopathology. Histopathologic assessment of the salivary glands plays an integral role in the diagnosis of primary Sjögren's syndrome. The procedure involves making a small incision in the lower lip to harvest at least 4-6 minor salivary glands with a minimum surface area of 8 mm^2 [261,262]. Hematoxylin and eosin staining help identify the presence of dense mononuclear cell (mostly lymphocytic) aggregates. The finding of foci of ≥50 mononuclear cells in a periductal or periacinal distribution, referred to as *focal lymphocytic sialadenitis*, is the most characteristic biopsy feature of primary Sjögren's syndrome with an 82.4% sensitivity and 82.6% specificity compared to other tests among patients with diagnosed SS [263]. A *focus score* (FS) is calculated by dividing the number of foci by the total surface area of normal appearing tissue, then multiplying by 4. A focus of ≥1/ 4 mm^2 of glandular tissue is considered consistent with the salivary component of SS [262,264]. The same definition of a positive biopsy has been included in all major classification criteria to date [249–251]

A large prospective cohort study, published in 2011, from the SICCA international tissue registry provides the most recent validation for use of the current FS diagnostic threshold [262]. The study examined the relationship between phenotypic features of SS and lip biopsy results in 3 different patient groups: 1) focal lymphocytic sialadenitis with FS ≥ 1/ 4 mm^2; 2) focal lymphocytic sialadenitis with FS ≤ 1/ 4 mm^2 and 3) other histologic patterns like chronic non-specific sialadenitis or sclerosing sialadenitis. The results demonstrated a significantly (all $p \leq 0.0001$) higher proportion of participants from group 1 (focal lymphocytic sialadenitis with FS ≥ 1/ 4 mm^2) vs. groups 2 and 3 among patients with positive serum anti-SSA/B antibodies (76%), rheumatoid factor (72%), antinuclear antibodies ≥1:320 (72%), keratoconjunctivitis sicca with OSS ≥3 (50%) and unstimulated whole salivary flow

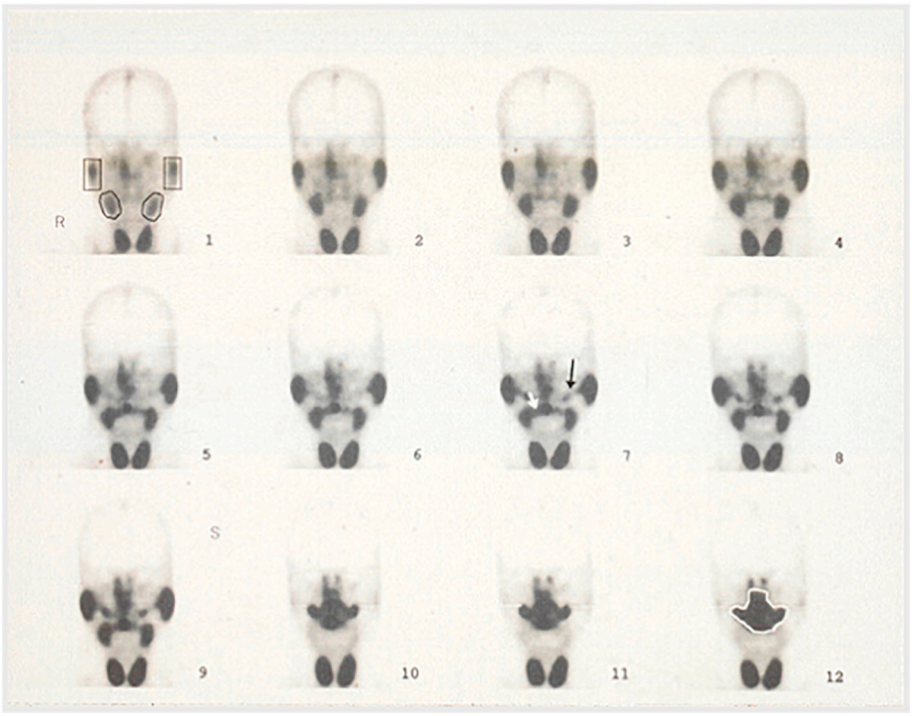

Fig. 1. Salivary scintigraphic images (5-minute frames) in a healthy individual demonstrate normal isotope uptake into the major salivary glands and thyroid (frames 1-5); resting discharge through Stenson's (black arrow) and Wharton's ducts (white arrow) (frames 6-9) and stimulated discharge following secretagogue administration (frames 9-12).

rates ≤0.1mL/min (53%). No significant association was found between any pattern on biopsy and symptoms of dry mouth or dry eyes [262].

Limitations of the labial minor salivary gland biopsy have been well-documented and include insufficient glandular tissue for histologic examination (which can lead to overestimation of the focus score), incorrect histologic interpretation of the local inflammatory infiltrate, and incorrect definition of a focus or lack of focus score quantification [265]. In addition, there is substantial variability in the surgical acquisition and processing of the salivary gland tissue [266,267]. Given these differences, expert guidelines for the standardized use of salivary gland histopathology for clinical trials and future SS research were issued in 2017 following a 2-day workshop sponsored by the EULAR Sjögren's Syndrome Study Group [261].

3.5. Imaging

3.5.1. Salivary gland ultrasonography

The use of salivary gland ultrasound (SGUS) in primary SS was first explored in the late 1980's [268]. Since then, ultrasound has been extensively studied as a diagnostic and monitoring tool in primary Sjögren's syndrome and is now considered the imaging modality of choice for the salivary glands [269,270]. The appeal of ultrasonography lies in its non-invasive approach, low cost, and potential for easy and readily accessible use. It is of a particular value in salivary gland assessment due to the superficial localization of the major salivary glands [270].

Findings in pSS identified on static ultrasound images of the major salivary glands include heterogeneous parenchyma defined as hypo- and anechoic areas with or without hyperechoic bands. In addition, the presence of intra-glandular calcifications, abnormal lymph nodes, and the absence of visibility of the posterior border of the gland, particularly for the submandibular glands, may also be seen. Notably, hyperechoic bands may also be seen in normal individuals due to aging or fibrosis of the glands, whereas heterogeneity within the gland is not a finding in normal glands. Among the different abnormalities seen, data obtained by experts in SGUS have shown that the two most reliable findings are echogenicity and homogeneity of both the parotid and submandibular glands [271].

Studies assessing the ability of SGUS to correctly identify Sjögren's versus other diagnostic modalities (including scintigraphy, sialography and salivary gland biopsy) have consistently demonstrated high specificity and diagnostic accuracy [272–275]. A recent review reported that most studies show a specificity ranging from 81.5%-98.7%. Sensitivity values, however, show much greater variability and range from 48%-91.4% [269]. Because of high specificity, ultrasound of the parotid and submandibular glands in recent years has gained popularity at many centers as a routine diagnostic study in patients with suspected SS [276,277].

Limitations in determining the validity of ultrasound in SS stem from an overall lack of uniformity between clinical studies, as well as the multitude of imaging abnormalities found. Factors that have added to this heterogeneity include variation in study design, brands of ultrasound equipment, probe frequencies, scanning techniques, and different scoring systems used [277]. This has limited attempts to standardize the procedure for inclusion in formal guidelines [277] and, thus far, no current classification criteria include SGUS for assessment of salivary gland involvement [249–251]. However, this may change in the future as both ACR and EULAR have issued position statements on ultrasound in rheumatology that acknowledge the value of SGUS in SS [276,278].

Additionally, a 2017 study by Le Goff and colleagues assessed the additional value that use of SGUS would add to existing classification criteria. They found that, when used as an alternative method for documenting objective evidence of salivary gland involvement and when given the same weight as unstimulated whole mouth salivary flow, Schirmer's test and ocular staining scores, ultrasound may improve the sensitivity of the 2016 ACR/EULAR classification criteria for pSS. With physician diagnosis as the reference standard, the inclusion of SGUS increased sensitivity from 87.4% to 91.1% while specificity remained high at 93.8%, compared to 95.4% without ultrasound [252]. This increase in sensitivity may allow additional patients with early primary Sjögren's syndrome who already have typical findings on salivary gland ultrasound, to be identified. The authors proposed that in patients with SSA antibody positivity, a typical salivary gland ultrasound may provide sufficient evidence to reasonably forego a salivary gland biopsy.

3.5.2. Magnetic resonance imaging

Findings on salivary gland MRI in Sjögren's evolve according to the duration and extent of disease. Early findings include enlarged parotid glands due to glandular edema from inflammation. As the disease progresses, lobular destruction may appear as small cystic changes associated with fatty replacement [269]. Patients with longer chronicity may show parotid gland atrophy and larger areas of cystic change including cystic destruction or lymphoepithelial cysts (similar to those seen in HIV-associated salivary gland disease). Progression of fatty replacement, as well as parenchymal calcifications and intra-parotid masses of lymph node aggregates can also be seen in advanced disease [246].

In the evaluation of a salivary gland mass, including lymphoma, MRI can help determine infiltration of adjacent structures and may be used for local staging. However, it does not always reliably distinguish benign from malignant lesions in early disease [269]. Therefore, a histologic diagnosis is required before treatment planning. An ultrasound-guided core needle biopsy under local anesthesia is preferable to fine needle aspiration and can easily be performed as an outpatient procedure [279].

3.5.3. Computed tomography

Imaging by CT is typically cheaper, faster, and often easier to obtain than MRI. However, exposure to ionizing radiation is a limitation that should be considered, and may be a drawback to its use. Similar to MR imaging, CT allows visualization of glandular enlargement due to inflammation in primary Sjögren's syndrome. In addition, non-contrast CT is particularly useful for the evaluation of sialolithiasis, a condition that also may present with salivary gland swelling [280].

While MRI is superior for assessing the extent of infiltration by glandular tumors into surrounding tissues, CT can sometimes differentiate between benign and malignant masses based on blood perfusion patterns and/or the presence of bony erosions [281]. Nevertheless, histologic confirmation is still required.

3.5.4. Sialography

Conventional sialography is a radiographic study that involves cannulation of Stenson's or Wharton's duct and injection of water-soluble iodinated contrast medium to visualize the anatomy of the ductal system [269]. Typical changes in ductal architecture related to chronic inflammation from Sjögren's syndrome include alternating ductal stenosis and dilatation. However, due to problems related to its invasiveness and radiation exposure, it is rarely used in clinical practice today except in cases of suspected ductal obstruction that cannot be confirmed by other imaging modalities [269,270]. Like scintigraphy, sialography was part of the 2002 AECG Sjögren's classification criteria, but was not included in more recent criteria sets because of these issues.

Sialo-CT and MR sialography are alternative modalities to visualize the ductal system. Although very expensive, MR sialography has the advantage of allowing better visualization of the parenchyma and small ductal branches without radiation or contrast. However, because saliva acts as the contrast agent in MR sialography, this may pose an issue in Sjögren's patients with severe xerostomia [270].

3.6. Proof of autoimmunity

At the present time, documentation of autoimmunity through serologic testing or demonstration of a positive labial minor salivary gland biopsy (see histopathology) comprise the 2 most reliable means to distinguish between primary Sjögren's syndrome and other diseases that cause sicca symptoms and salivary gland swelling. Antinuclear antibodies (ANA) and rheumatoid factor (RF) are the two most prevalent autoantibodies in SS but generally are not used for diagnosis or classification criteria due to lack of specificity [158,282]. Most criteria or diagnostic algorithms require demonstration of the Sjögren's marker autoantibodies, anti-SSA/SSB. The only exception to this view occurred in 2012 with publication of the ACR-SICCA classification criteria [34] where it was suggested that the co-occurrence of RF (any titer) and ANA $\geq$1:320 (any pattern) could be utilized as serologic proof of SS in the absence of anti-SSA/SSB positivity. This was based on findings from a 2011 study described above that showed a significant association between the characteristic histologic pattern of SS (focal lymphocytic sialadenitis with FS $\geq$1/ 4 mm^2) and RF and ANA positivity [262].

When present, the marker autoantibodies for SS may occur in one of 3 different patterns: anti-SSA/SSB, anti-SSA alone or anti-SSB alone. The first 2 patterns are common while the last one is rare. Both forms of anti-SSA antibodies may occur together or separately in SS and recognize either the Ro 52kD or the Ro 60kD antigens. The relative prevalence and clinical associations of each form of anti-SSA vary according to the assay methods used and the populations tested [282–284].

Anti-SSB most frequently occurs with anti-SSA due to shared epitopes, and rarely occurs alone. In the SICCA registry, among 3297 participants tested for autoantibodies, isolated anti-SSB occurred in only 2% of cases. Despite its rarity, isolated anti-SSB was included in the 2002 and 2012 classification criteria as proof of autoimmunity for SS. However, it was purposely excluded from the 2016 ACR-EULAR criteria following a study by Baer and coworkers from the SICCA registry [285] that examined the phenotype of the above group with isolated anti-SSB. The study showed that despite the equal occurrence of sicca symptoms, the anti-SSB group bore little resemblance to patients who were anti-SSA or anti-SSA/SSB positive. The majority of lip biopsies (74%) performed in the anti-SSB group were also negative. It was also observed that a change in autoantibody assay procedures during the registry from the initial Bio-Rad Autoimmune EIA (Bio-Rad, Hercules, CA) to a Bio-Rad Bioplex 2200 multiplex flow immunoassay created a 10-fold increase in the number of anti-SSB positive results. This suggests that many of these results are false positives that arise as an artifact of newer automated assay procedures.

Prior studies have shown that anti-SSA may occur in 1.7-17.5% of normal individuals depending on the assay procedures used and the populations tested [284,286]. A Swedish registry and health-care biobank study also reported that anti-SSA and other autoantibodies may appear in the blood of SS patients up to 20 years before the actual diagnosis [286]. Thus, the presence of an autoantibody (even anti-SSA) as a stand-alone test is insufficient to confirm the diagnosis of SS without objective evidence of dryness.

A variety of other autoantibodies have been described in Sjögren's as recently reviewed [287,288]. At least 3 of these novel antibodies are commercially available: anti-salivary protein 1 (anti-SP-1), anti-carbonic anhydrase 6 (anti-CA 6) and anti-parotid secretory protein (anti-PSP). These antibodies were discovered in the IL-14α transgenic mouse model of SS [289] and shown to be markers of early disease. They appear in the blood of these animals before anti-SSA/SSB antibodies, and before lymphocytic infiltration of the salivary glands occurs [290]. Anti-CA 6 and anti-PSP recognize proteins found in both murine and human salivary glands. The biological function of the antigen recognized by anti-SP-1 remains unknown. However, recent work demonstrated shared epitopes with antigens found in human parotid glands [291]. These novel murine autoantibodies have also been detected in the non-obese diabetic mouse model of SS, in humans with established SS who meet AECG criteria, in humans with SS who are biopsy positive but SSA/SSB negative, and in patients with idiopathic dry eyes and mouth of less than 2 years' duration [290]. Anti-SP-1 may also be a marker for secondary SS in patients with rheumatoid arthritis [291]. Despite these promising results, however, further studies in larger patient cohorts including healthy controls, patients with other connective tissue disorders and SS patients at various stages of the disease are needed before this novel murine autoantibody panel can be regularly used in practice.

3.7. Moving toward diagnostic criteria

At the present time, due to the lack of universally accepted diagnostic criteria for SS, clinicians are frequently left scratching their heads and forced to use classification criteria by default to make a diagnosis. Although the differences between criteria can be confusing, they always aim to satisfy 3 basic objectives. The first 2 goals are to demonstrate objective evidence of dry eyes and salivary gland involvement. The third involves proof of autoimmunity which helps differentiate SS from numerous other causes of dryness and salivary gland swelling as described below. In a practical sense, given the high specificity (≥90%) of the aforementioned classification criteria, any patient who meets at least one of them can be confidently diagnosed with SS. It must be remembered, however, that classification criteria frequently sacrifice sensitivity in favor of specificity. Therefore, in a clinical setting, any patient with a positive anti-SSA antibody or lip biopsy who demonstrates objective evidence of dryness should also be diagnosed with Sjögren's once other diseases or conditions that cause similar symptoms have been excluded. In doubtful cases, the physician's clinical judgment always remains the gold standard for diagnosis. Our current approach to diagnosing SS in patients with unexplained sicca symptoms or extraglandular manifestations in the clinical setting is outlined in Table 5.

3.8. Differential diagnosis

While we recognize the high degree of variability in the clinical presentations of Sjögren's syndrome, ranging from sicca symptoms to largely asymptomatic patients to individuals with severe organ-specific involvement and high systemic disease activity, a discussion about the differential diagnosis of SS for the purposes of this article will intentionally be limited to that which pertains to the salivary glands.

Medication-induced xerostomia remains the most common cause of the sicca syndrome, especially in the setting of polypharmacy [292,293]. Other diagnoses that should be considered in patients with dryness and/or salivary gland enlargement include sialolithiasis (calculus disease), sialadenosis (fatty infiltration) and chronic sialadenitis. Sialadenosis, or sialosis, typically causes painless symmetric glandular enlargement with mild sicca symptoms and results from a variety of causes including the metabolic syndrome, malnutrition, medications (e.g. chronic steroid use) and alcoholism [294,295]. Chronic sialadenitis is a scarring disorder of the salivary glands that can cause severe dryness and is frequently associated with osteoarthritis [296]. Patients who undergo external beam irradiation for head and neck tumors, or radioactive iodine treatment for Graves' disease or thyroid cancer may also develop sicca symptoms and glandular swelling from obstruction.

Table 5
Clinical diagnosis of Sjögren's syndrome.

1. Anti-SSA positivity *or* RF[a] + ANA (> 1:320)[b] positivity (choose 1)
2. Positive lip biopsy (focal lymphocytic sialadenitis with FS ≥ 1/4mm^2)
3. Objective evidence of dry eyes (any 1)
   a) Abnormal Schirmer's test (≤ 10 mm/5 min)
   b) Any abnormal ocular surface staining using vital dyes (i.e. rose bengal, fluorescein, lissamine green)
4. Objective evidence of salivary gland involvement (any 1)
   a) Abnormal whole mouth salivary flow rate (< 0.3 ml/min)[c]
   b) Abnormal scintigraphy (defect in ≥ 1 of 3 phases of salivary gland function i.e. uptake, secretion, stimulated function)
   c) Typical appearance on salivary gland ultrasonography
   d) Typical appearance on CT/MRI of the major salivary glands

Diagnosis requires fulfillment of ≥ 3 of 4, and exclusion of prior head & neck irradiation, HIV, active hepatitis C infection (confirmation by PCR), graft vs. host disease, acquired immune deficiency syndrome, sarcoidosis, amyloidosis, IgG4-related disease and use of drying medications.

[a] Any titer.
[b] Any pattern.
[c] Abnormal result.

Sialadenitis may also result from a variety of infectious organisms [297,298]. Individuals with acute HIV, and/ or hepatitis C infection may develop a clinical syndrome with dryness, swollen salivary glands and rheumatic symptoms that is almost indistinguishable from primary SS [299,300]. In addition to Sjögren's syndrome, other autoimmune inflammatory processes that can affect the salivary glands include IgG4 disease and sarcoidosis [301,302].

Determining the etiology of salivary gland disease can sometimes be suggested on the basis of the patient's clinical history and the physical examination. Attention should be paid to the acuity of symptom onset, presence of pain, presence of associated symptoms (such as a viral prodrome) and whether one or both sides are affected. Sialolithiasis and bacterial sialadenitis are often painful and acutely affect the glands unilaterally, whereas non-bacterial infectious or autoimmune causes of sialadenitis can present acutely or over a longer period of time, and typically involve glands on both sides [246]. Additionally, patients with salivary gland stones often develop swelling of the affected parotid gland after chewing or eating. They may be aware of past episodes that resulted in the passing of stones or gravel in the mouth when the swelling subsided. Patients with bacterial sialadenitis may become febrile and develop erythema surrounding the involved site.

In addition to laboratory evaluation looking for specific etiologies, imaging studies may further be able to aid in diagnosis. Unenhanced CT is recommended as the diagnostic test of choice for evaluation of salivary gland stones given its improved sensitivity over radiography for detecting calcifications, obstructing masses and associated inflammatory changes [246]. If additional imaging is necessary in the absence of a visualized stone, MR sialography may be able to identify a previously missed calculus and provide an overview of the salivary gland ductal anatomy as a whole. Salivary gland infections typically appear as non-specific glandular enlargement and fat stranding, and may have associated thickening of the superficial cervical fascia and platysma muscle. Attention should be paid to look for the presence of an abscess or large calculus, particularly in the setting of a bacterial infection, as these may require additional treatment such as drainage or surgical removal. HIV-associated salivary gland disease has a more characteristic finding of benign lymphoepithelial cysts (BLECs) which can cause gradual onset of painless bilateral salivary gland enlargement [303]. Sarcoidosis affecting the salivary glands can manifest as granulomatous lymph node aggregates which appear as nonspecific intraparotid masses, and IgG4 plasma cell infiltration appears as nonspecific homogeneous enhancement of an enlarged gland [246,301,302].

3.9. Summary

The clinician is confronted with many challenges when evaluating a patient for possible Sjögren's syndrome. These include a wide spectrum of clinical presentations, an expanding list of differential diagnoses, lack of universally accepted diagnostic criteria and a bewildering array of diagnostic studies and algorithms from which to choose. A focused evaluation to document objective evidence of dry eyes, objective evidence of salivary gland involvement and proof of autoimmunity is most important. At the present time demonstration of anti-SSA positivity and/or histologic involvement with focal lymphocytic sialadenitis and a focus score ≥1/ 4 mm^2 provide the most reliable means to distinguish between SS and its various mimics. The recent development of new classification criteria should facilitate more clinical trials in the future. The emergence of new diagnostic techniques including salivary gland ultrasonography and the identification of novel biomarkers should move the field forward and, hopefully, simplify diagnosis in the future.

Understanding what SS is requires appreciation of the genetic, environmental and immunological factors that contribute to its existence. The next section will discuss known genetic factors contributing to the development of SS.

4. Genetics

4.1. Introduction

Over the past several years, genetic studies in SS have greatly expanded from hypothesis-driven testing of candidate genes in relatively small sample sizes, to much larger unbiased genome-wide association studies (GWAS) made possible by revolutionary advances in genotyping technologies. Evaluations in populations from European and Asian ancestry have confirmed previously recognized associations with *HLA-DR* and *-DQ* alleles as well as established strong associations with multiple new genetic risk loci [304]. An important caveat to the powerful GWAS approach is that the variant most associated with increased risk of SS is likely to be a marker for a linked causal allele that has yet to be determined. Subsequent functional studies showing how the risk allele alters biological function are required to establish the precise SS risk variant. However, we know that both innate and adaptive immune functions are clearly affected by various SS risk variants. Many of the SS risk genes identified to date are involved in interferon responses, lymphocyte migration, cytokine and cytokine receptor function and various other intracellular signaling pathways that are important in multiple immune cell subsets.

4.1.1. Antigen presentation and epithelial cell function

The strongest and most consistent genetic predisposition to SS is driven by the Major Histocompatibility Complex (MHC) region that harbors the human leukocyte antigen (*HLA*) genes. Associations have been identified with different Class II alleles that vary by population and serological status [305,306]. The *-DR2* and *-DR3* alleles at *HLA-DRB1* have consistently been associated in Caucasian populations [20,307]. Meta-analysis of 23 studies from diverse ethnic backgrounds confirmed that significant risk was associated with HLA Class II alleles *DRB1**03:01, *DQA1**05:01, and *DQB1**02:01 [308]. Another large-scale study found two highly significant associations [309]. The first was with an extended 5 mega base (Mb) haplotype peaking at *HLA-DQB1* but also including Class III and I, in addition to a second independent association effect that was localized to a narrow region peaking at *HLA-DQA1*. Associations with *HLA-DRB1/HLA-DQA1* and *HLA-DPB1* have been established in Han Chinese and other Asian SS patients [306,310]. In general, associations in the HLA region tend to be even stronger when serological status is considered. For example, associations of anti-SSA and/or anti-SSB production with *DRB1**03 and *DQB1**02 alleles or with heterozygosity for *DQw1* and *DQw2* alleles are exceptionally strong [311]. Interestingly, multiple HLA genes on the extended 5 Mb haplotype were comprised of risk alleles that altered mRNA expression levels, suggesting that the HLA region potentially confers risk through multiple pathogenic mechanisms. The loci with expression differences revealed when subjects were stratified by genotype included Class II *HLA-DRB6*, *-DPB1*, *-DQA1* as well as Class I *HLA-C* and *-A*.

Further contribution of the MHC region to risk of SS has been reported from a non-canonical MHC-linked locus that is independent of the HLA associations. This locus encompasses the Class I polypeptide-related sequence A *(MICA)* gene. *MICA* is a highly polymorphic gene that is expressed in epithelial cells and encodes a stress-induced glycoprotein recognized by the natural killer group 2D (NKG2D) receptor expressed on various subsets of $CD4^+$ T cells, $CD8^+$ T cells and natural killer (NK) cells [312,313]. Strong association of the MICA*008 allele with SS has been found in two European cohorts [314]. The risk allele is associated with increased levels of stress-inducible MICA protein in serum and may contribute to shared pathogenic pathways involved in reduced protection against cancer and autoimmunity.

4.1.2. Interferon responses

Dysregulation of innate immunity has been demonstrated by studies of salivary glands and peripheral blood from SS patients. Increased transcription of IFN-inducible genes, referred to as the “IFN signature”, is strongly correlated with high titers of anti-SSA and anti-SSB [309,315,316]. The contribution of genetic risk variants to this signature has been supported by the identification of association with multiple genes that are involved in IFN responses, including interferon regulatory factor 5 (*IRF5)*, signal transducer and activator of transcription 4 (*STAT4)*, interleukin 12A (*IL12A*) and 2′-5′ oligoadenylate synthetase 1 (*OAS1*).

IRF5 is the strongest association identified to date outside the MHC region. This transcription factor is responsive to signaling through toll-like receptors (TLR) and the type I IFN receptor (IFNAR) to promote the expression of anti-viral and pro-inflammatory proteins [317,318]. *IRF5* is associated with SS in all ancestries evaluated to date, with the most significant association being found for a promoter region CGGGG insertion/deletion (indel) polymorphism [319–322]. A second independent effect has been identified in European-derived populations that results from a haplotype of linked variants spanning both *IRF5* and the neighboring gene, transportin 3 (*TNPO3*) [323]. A recent model suggests that within this haplotype, the risk allele confers increased binding of the transcription factor ZBTB3 to the *IRF5* promoter, resulting in upregulated *IRF5* expression [324].

STAT4 is a transcription factor that is activated by type I IFN, IL-12, and IL-23 [320,325–327]. Additive effects between the major risk alleles in *IRF5* and *STAT4* have been reported [320,327]. IL12 is an immunomodulatory cytokine primarily secreted by dendritic cells and monocytes. Acting upstream of STAT 4, IL12 plays an important role in Th1 cell differentiation and production of IFN-γ by T cells and NK cells [328]. The *IL12A* gene encodes a p35 subunit that forms a heterodimer with a p40 subunit encoded by *IL12B* [329]. The risk attributable to the *IL12A* gene appears to be stronger in Europeans than in Asians [306]. *OAS1* is a type I IFN-induced gene often directly observed as overexpressed in the IFN signature. Interestingly, a risk variant has been identified that alters splicing, and shifts expression of the p46 isoform to alternative transcripts that lack translational response to type I IFN stimulation. At the protein level, the risk variant of *OAS1* is associated with decreased OAS1 enzymatic activity and viral clearance [330]. Furthermore, overexpression of *OAS1* transcripts appears to be amplified by presence of anti-SSA. The pathogenic mechanism for how this variant contributes to SS is currently unclear.

4.1.3. Other innate immunity factors

B-cell activating factor (BAFF/BlyS) is central to the crosstalk between innate immunity and stimulation of autoreactive B cells. BAFF is typically produced by monocytes, macrophages and dendritic cells. However, in patients with SS, T and B cells can also produce BAFF as well as salivary epithelial cells [331]. The production of BAFF has been shown to be inducible by type I and II IFNs. Protein levels of BAFF are increased in serum of SS patients compared to healthy controls, and are highly correlated with disease activity and titer of circulating autoantibodies [332–337]. Candidate gene studies of *BAFF* and *BAFF-R* support association of a haplotype consisting of four linked SNPs located in the 5’ regulatory region of the *BAFF* gene in patients that are positive for anti-SSA and anti-SSB. A different haplotype has also been associated with SS in patients with lymphoma compared to healthy controls [337,338].

Cytotoxic natural killer (NK) lymphocytes play a critical role in innate immunity. Based on evidence for a potential role of NK cells observed in animal models of sialadenitis, a candidate gene study of *NCR3/NKp30* was performed that showed association of SS with promoter SNPs. These findings support a potential role for NK cells through promoting an NKp30-dependent inflammatory state in salivary glands [339,340].

4.1.4. B Lymphocyte function

Complex dysregulation of adaptive immune responses clearly contributes to the pathogenesis of SS. Several genetic associations have been established for genes involved in B cell function. Two SNPs in

Early B-cell factor 1 (*EBF1)*, a key transcription factor involved in B cell development, are associated with SS and changes in expression levels of *EBF1* can lead to impairment of B cell development [323]. B cell function in SS is also thought to be affected by variants in a promoter with dual transcriptional control for both the *FAM167A* and the *BLK* (B lymphocyte kinase) genes. Association at this locus was first found in a candidate gene study of Swedish and Norwegian populations, and later replicated in other European and Asian cohorts [309,319,320,323,325]. *FAM167A* and *BLK* are transcribed in opposite directions from a common promoter, and interestingly, have expression levels that are inversely correlated. *FAM167A* encodes DIORA-1, which is highly expressed in the lung and may have a potential role in pulmonary involvement [341]. *BLK* plays a major role in B cell signaling through activation of multiple nuclear transcription factors. Risk of SS through reduced expression of *BLK* may lead to breaks in tolerance by allowing autoreactive cells to escape depletion [323]. In addition, a novel association of SS with a SNP located upstream of the coding region of *CXCR5* has been described [309]. Dysregulated expression of *CXCR5* has been shown in B cells from the periphery and in salivary gland tissues [342,343]. The SS risk allele of *CXCR5* correlates with decreased expression of CXCR5 in peripheral blood B cells, low numbers of $CXCR5^+$ peripheral blood B cells, and homing of $CXCR5^+$ B cells to the minor salivary glands [344].

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) protein complex is found in almost all eukaryotic cell types and has a central role in rapid regulation of transcriptional responses to harmful cellular stimuli. Chronically active NF-kB signaling is found in numerous inflammatory diseases. Two genes that regulate NF-kB pathways have been associated with SS. Risk variants in tumor necrosis factor-alpha-induced protein 3 (*TNFAIP3*) have been associated with increased risk of lymphoma in SS [345], possibly through dysregulation of ubiquitination. TNFAIP3-interacting protein (*TNIP1*) has also been associated with SS [346]. *TNIP1* cooperates with *TNFAIP3*, which in turn suppresses toll like receptor (TLR)-induced apoptosis by negatively regulating NF-kB [347,348]. To date, the precise cell types affected by dysregulated NF-kB signaling in SS are unclear but likely to be complex and work mechanistically through pathogenic alterations in TNF-induced apoptosis, TLR4 activation, or cytokine production.

4.1.5. Chromosome X

Speculation on the cause of the remarkable gender disparity in SS (14:1 female: male ratio) has implicated numerous factors including anatomy, lifestyle, and sex hormones with very little data to directly support these hypotheses [349]. Recent studies of the X chromosome have suggested that a viable alternative explanation is that the number of X chromosomes increases the likelihood of developing SS, potentially through a gene dosage mechanism.

Men with Klinefelter´s syndrome (47, XXY) have a similar risk of developing SS as normal 46, XX women [349]. In addition, the estimated prevalence of SS in women with 47, XXX is ~2.9 times higher than that in those with 46, XX [350]. The coexistence of Turner syndrome (45, X) with SS is very rare. In studies of rare aneuploidies, structural chromosomal aberrations resulting in partial triplications of the X chromosome (Xp11.4 ::pter) have been described in 3 patients with SS, suggesting that dosage-sensitive risk genes may be located within this chromosomal interval [351]. Numerous genes with a role in immunological processes serve as interesting candidates, however the causal gene(s) that mediate this effect are as yet unclear.

4.1.6. Associations in Asian populations

Several genes appear to be associated in Asian populations that have yet to be confirmed in other groups. In a GWAS of Han Chinese, a novel association with a region spanning *GTF2IRD1-GTF2I* [310] was reported and later replicated in an independent GWAS of Taiwanese Han Chinese SS females. The potential biological role for either of these genes in SS pathogenesis is unclear. Another association that seems to be specific for Asians has been identified with killer cell lectin-like receptor, subfamily G, Member 1 (*KLRG1*) [306]. *KLRG1* is expressed in peripheral blood NK cell and monocytes and binds to NF-kB complex proteins in B cells. Associations with *IKZF1* have been reported in two studies [306,352]. *IKZF1* is a transcription factor that regulates lymphocyte differentiation and interestingly, shares common interaction partners with *GTF2I* that are involved in histone deacetylation [306,352].

4.1.7. Future genetic studies

In summary, large-scale genetic studies to date have been remarkably successful in establishing associations that are convincing and lend insight into the complex etiology of SS in individuals of European and Asian origin. There are dozens of additional strong candidate genes that have shown suggestive levels of association for which follow-up studies are warranted. Ongoing studies are aimed at precisely localizing the causal variants within the regions thus far associated with SS, determining biological consequences such as the effects on cellular functions and contribution to clinical manifestations, understanding similarities and differences between the genetic architecture of various racial populations, and identifying additional novel associations. The genetics of SS are substantially understudied compared to other systemic autoimmune diseases and will require continued effort to develop a comprehensive understanding of the underlying risk factors. To advance the field further, continuing to apply powerful genetic and genomic tools to increased sample sizes will be critical for gaining the statistical power needed to identify additional associations and begin to understand how these risk variants operate in various patient subsets.

4.2. Immunological and cell biological aspects

Based on the extensive pathology and histology now accumulating from SS patient biopsies and tissues, there is a strong consensus that SS syndrome is a systemic autoimmune disease. Nevertheless, confounding factors, such as viral infections, anti-cholinergic drugs, radiation therapy, aging and other systemic inflammatory diseases known to cause pathology very similar to SS, must be excluded from any final diagnosis. This is not a simple task considering the widespread distribution in humans of hepatitis B, hepatitis C, HTLV-1, mumps and CMV, or rheumatoid diseases, sarcoidosis, irradiation, and environmental factors [353]. Confounding this even further is the fact that organ damage can be demonstrated in the presence of (auto)antibodies, but absence of detectable T and B lymphocytes, not unlike what can be seen in other autoimmune diseases, e.g., type 1 diabetes and rheumatoid arthritis [354,355]. These data and observations, when considered together, suggest that (a) loss of salivary and lacrimal gland function can occur prior to detection of lymphocyte infiltration in the glandular tissue, and (b) lymphocyte-directed killing of the target organ is not necessarily a major factor, at least in some patients, during the early course of disease. However, it does appear that an adaptive immune response is a major feature in the later stages of disease. Thus, critical questions remain in defining the mechanism(s) by which organ injury occurs (Fig. 2).

The prevalence of autoantibodies, especially ANAs that are used to define SS as a disease entity, point directly to the importance of B lymphocytes in SS. However, both B lymphocytes and antibodies have many immunological functions and it would be expected that this is the case in SS as well. Studies in various autoimmune diseases have suggested that some autoantibodies, especially IgM autoantibodies, may be utilized by the immune system to recognize damaged tissues and recruit cells that participate in tissue repair [356,357]. If tissue inflammation is downregulated prior to loss of function in the targeted tissue, any overt autoimmunity would most likely go un-noticed or un-diagnosed. Perhaps what defines development of SS and other autoimmune diseases is the inability to control tissue inflammation, thereby establishing the correct environment for this innate response to activate an adaptive

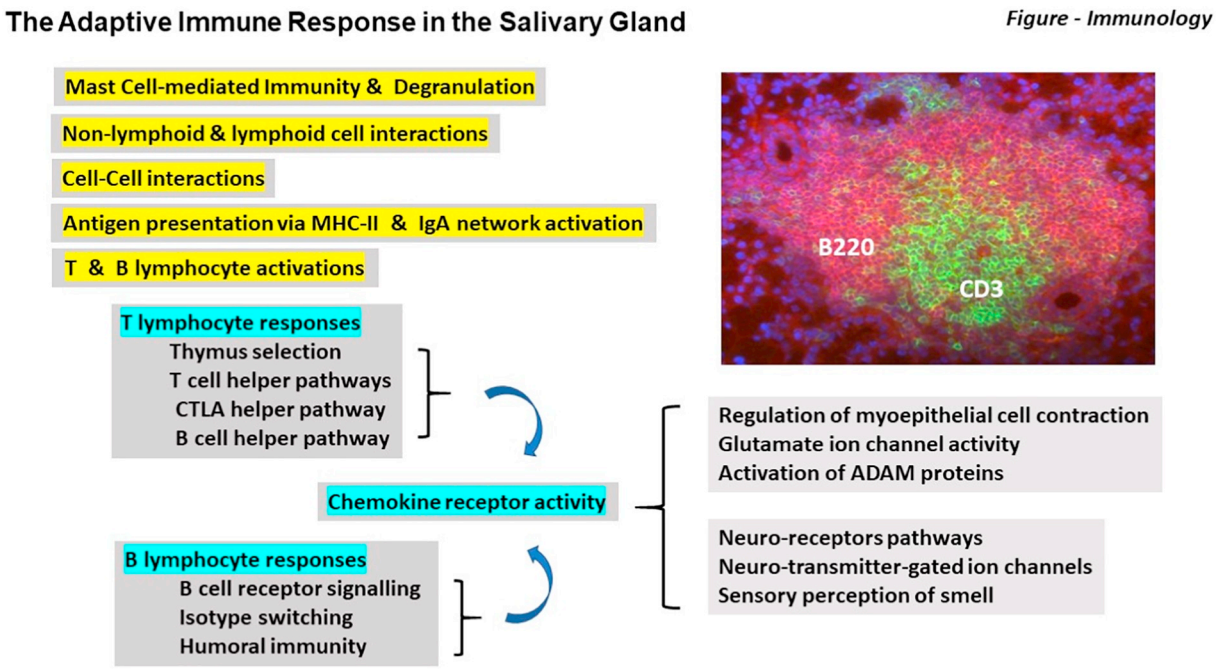

Fig. 2. The adaptive immune response profile in the salivary glands of C57BL/6.NOD-*Aec1Aec2* mice. Concomitant with the loss of salivary flow rates, lymphocytic foci appear within the periductal exocrine tissue of the glands. The early lymphocytic foci (LF) are generally a core of T cells surrounded by large accumulations of B cells (photomicrograph). Global gene micro-arrays reveal a set of genes upregulated coordinate with the time of LF appearance, and these genes identify biological functions (yellow highlighted text) that indicate: (a) antigenic peptides are being presented by antigen-presenting cells in a MHC class II manner, (b) the majority of T cells are T-helper cells, (c) B cell receptors are being activated with concomitant Ig class switching, leading to B cell-mediated cytotoxicity, and (d) mast cells apparently are activated and undergo degranulate. The overall consequence of the adaptive immune response is the loss of neural activity and secretion. The connection between the immune response and the neural response, apparently linked functionally by chemokines, raises the question of whether the source of the chemokines is the glandular tissue *per se*.

immune response characterized in part by conversion of a normal low affinity autoreactivity to a high affinity autoimmune response that (a) is capable of injuring self-tissue(s) (e.g., IgG autoantibody-mediated cytotoxicity) and (b) activating memory B and T cells less susceptible to growth inhibitory and apoptotic signals than primary lymphocytes [358,359]. Similar to T1-diabetes and SLE, a subset of SS patients produces autoantibodies years before clinical disease becomes evident [360,361], an observation that raises the possibility that these patients may be responding to an environmental challenge that could be controlled long-term prior to a breakthrough to an overt disease. All normal individuals appear to produce autoantibodies, just not in the titers, isotypes and affinities seen in patients with autoimmune diseases. It seems logical to assume that SS-susceptible individuals have a genetic predisposition that fails to downregulate an innate and/or adaptive immune function to a specific environmental trigger(s).

The importance of B cells and their products in SS has been strongly supported by the work of Peck and colleagues in a mouse model of SS in which silencing the Ig-mu gene resulted in the lack of mature B lymphocyte development and the subsequent lack of a SS-like disease development [362]. However, as with human SS, it remains unknown if the SS-like disease in these mice is the result of autoantibody production or another B cell function. The use of animal models in the study of SS has several caveats. On the plus side, animal models of spontaneous SS-like disease permit studies of the time course for disease-associated pathophysiological changes, the influence of inducing specific genetic changes on the disease process, and the outcome of therapeutic strategies. Animals can be autopsied to assess the status of organs at specific stages of disease, especially during the preclinical stages which can almost never be appreciated in SS patients. On the negative side, SS is a heterogeneous disease, therefore each animal model likely represents a single form of disease that may be present in some, but not all patients. In addition, depending on how an animal model is established, the cure for the disease may merely involve reversing the mechanism by which the disease was induced, undermining the relevance to treating human disease. Lastly, animals often respond immunologically different than humans to environmental challenges, thus not all observations made in animals are translatable to human disease. In any event, observations made in animal models of SS need to be reassessed in SS patients, when possible [363,364].

While several recently published reviews have described more than 30 mouse lines that have been used to study SS, the vast majority of these 'models' fail to exhibit critical manifestations of SS, i.e., loss of salivary and lacrimal glandular functions [363,365,366]. The first murine models used to study SS were mice being utilized to study SLE [16]. The (NZB X NZW)F1 mouse, which develops features of SLE, was important to identify genes involved in the pathogenesis [367], even though these mice do not develop sicca symptoms naturally. However, this mouse model can be induced to develop SS-like symptoms using Toll-like receptor 3 (TLR3) agonist known to activate production of type 1 interferons [368]. Similarly, the MRL/lpr mouse, which expresses a mutation in Fas and therefore in reality represents a model for human lymphoproliferative syndrome [369], has been used as a model for SS. These mice develop lymphocytic infiltrations of salivary glands and produce anti-Ro antibodies, but they fail to develop either keratoconjunctivitis sicca or loss of salivation [370].

The first murine model identified to naturally develop salivary and lacrimal gland dysfunction consistent with SS was the NOD mouse [371]. While these mice were shown to develop both a type 1 diabetes (T1D) and SS-like disease, the two autoimmune diseases were shown to result from different genetic regulation. Importantly, the T1D phenotype has been shown to involve more than 20 chromosomal regions with a strong dependence on the major histocompatibility complex, whereas the SS-like phenotype is far more permissive, a feature that has permitted separation of the two diseases [372,373]. This was first demonstrated in the NOD.B10Sn-*H2*^{b}/J mouse derived by replacing the MHC locus of the NOD mouse with the MHC of the C57BL/6 strain.

These recombinant inbred (RI) mice do not develop T1D, but continue to develop SS-like disease characterized by lymphocytic infiltration of the salivary and lacrimal glands, as well as pulmonary disease, renal disease and autoantibodies [374,375]. Similarly, deleting Toll-2 from the NOD mouse genome eliminates T1D without affecting development of SS [376], while blocking intracellular adhesion molecule-1 (ICAM-1) early in the course of the disease prevents the salivary gland inflammation without affecting T1D [377], indicating the critical role of non-MHC genes in these two diseases.

These early observations indicating that SS-like pathology of the NOD mouse was dependent on non-MHC genes led to work designed to identify those genetic regions of the NOD mouse regulating onset of the SS-like phenotype. Two genetic loci derived from the NOD strain, *Idd3* (renamed autoimmune exocrinopathy-1, or *Aec1*) located on chromosome 3 and *Idd5* (renamed *Aec2*) located on chromosome 1, were identified and bred into the C57BL/6J mouse, a non-autoimmune parental strain being used at that time for most genetic studies. The resulting RI mouse strain, named C57BL/6.NOD-*Aec1Aec2*, failed to develop T1D, but demonstrated loss of salivary gland function prior to and concomitant with lymphocytic infiltrations of the exocrine glands, lung and kidney tissues, plus B and T cell activation, as well as autoantibody and inflammatory cytokine productions [378,379]. Importantly, temporal genomic-wide microarray analyses of the salivary and lacrimal glands from C57BL/6.NOD-*Aec1Aec2* mice have defined the various genes and gene sets exhibiting differential activations during development and onset of the SS-like disease at the molecular level with results indicating a strong IFN-signature [380].

Identification of an IFN signature in the C57BL/6.NOD-*Aec1Aec2* mouse is not only in-line with studies in SS patients, but also suggestive that the environmental trigger could be a virus [381–383]. Over several decades, researcher have hypothesized that development of SS is initiated by a viral infection of the salivary and/or lacrimal glands that leads to the initial tissue injury that sets off the disease process in individuals with the appropriate genetic background [384]. In a study by Ohyama et al. [385], C57BL/6-*lpr*-deficient mice (C57BL/6.*lpr/lpr-/-)* were infected with a murine cytomegalovirus. The mice not only developed sialoadenitis that persisted even after the infection was cleared, but also a chronic inflammation with T cells and high titers of anti-Ro antibodies. In a different approach, Peck and colleagues performed a genetic analysis of the IFN-signature seen in C57BL/6.NOD-*Aec1Aec2* mice concluding that the IFN-signature *per se* indicated the inflammatory response was directed toward a dsRNA entity [386]. However, the concept of a viral trigger for SS is far from being resolved.

Results from extensive studies of SS in both humans and murine models establish a firm basis for SS being an intriguing autoimmune disease, thus understanding the disease requires understanding the immune response against the salivary and lacrimal glands per se and the immunological involvement of other tissues such as the lungs and kidneys. Clearly many different cell types are involved. For example, in patients with SS, increased expression of BAFF in epithelial cells has been proposed to be responsible for the abnormal activation of B cells and survival of autoreactive B cells [387]. The BAFF transgenic mouse model develops a disease similar to human SS including a proliferative glomerulonephritis [388]. While these BAFF transgenic mice do not normally develop lymphoma, they do so if lacking the TNF-α gene [389]. Furthermore, BAFF transgenic mice lacking marginal zone B cells fail to develop features of SS, even though they still develop glomerulonephritis [390], an observation that implies that MZB cells, which are capable of producing lymphotoxin [391], are critical for the development of SS [392,393]. It also demonstrates that various clinical features in an animal with systemic autoimmunity may not all have the same pathogenesis.

As stated above, one of the most interesting hallmarks of SS is the high risk for B cell lymphomagenesis. One hypothesis for this phenomenon is that development of autoimmune disease converts low affinity autoreactivity to a high affinity memory response driven by various cytokines. Recent in-depth studies by Ambrus and colleagues using an Interleukin-14 (IL-14) transgenic mouse model [394] have shown that these mice not only develop features of SS seen in patients, i.e., hypergammaglobulinemia, autoantibodies, loss of salivary gland function, lymphocytic infiltration of the submandibular and lacrimal glands before the parotid glands, lymphocytic interstitial lung disease, and mild renal disease, but also develop large B cell lymphomas late in life. Except for early-stage loss of salivary gland function and lymphocytic infiltration of the submandibular and lacrimal glands, these observed pathological features, including B cell lymphomagenesis, could be eliminated by deletion of marginal zone B cells, lymphotoxin or the *Ifn1* receptor gene [395]. Essentially, a continuous production of IL-14 appears to drive this abnormal memory B cell function by providing a long-term opportunity for B cell transformation. Interestingly, while MRL/lpr, (NZB x NZW) F1 and C57BL/6.NOD-*Aec1Aec2* mice produce IL-14 at high levels, studies of C57BL/6.NOD-*Aec1Aec2* mice have shown that mice downregulate IL14 production once its SS-like disease has matured, resulting in no B cell lymphomagenesis (Ambrus and Peck, unpublished data).

A major characteristic of SS observed in patients is a severe hypergammaglobulinemia. As with many other autoimmune diseases, the appearance of autoantibodies to the targeted organs, in this case, salivary and lacrimal gland antigens, salivary gland protein-1, carbonic anhydrase-6 and parotid secretory protein, can occur before clinical disease [291] or even the detection of anti-nuclear autoantibodies like Ro used in disease diagnosis [396]. These observations have been confirmed in both mouse models for SS as well as in patients [397–399]. In fact, Scofield et al. [400] were able to generate these autoantibodies via immunization of SS-non-susceptible BALB/c mice, leading to decreased salivary gland flow rates and lymphocytic infiltrations of the salivary glands. While lymphocytes was noted, no lacrimal gland disease nor disease of the lungs, kidneys or lymph nodes were noted [401]. Similarly, anti-muscarinic receptor 3 antibodies are seen in a subgroup of patients with SS. T cells from C57Bl/6-M3R-/- mice immunized with M3R peptides transferred into C57BL/6-Rag-1-/- mice caused decrease in salivary flow and infiltration of the salivary glands with lymphocytes [402].

Yet despite the clear role for inflammation in the pathophysiology of Sjogren's there has been a lack of correlation between salivary flow and infiltration and tissue damage within the gland. Many patients display low inflammation but substantial loss of gland activity [403]. Salivary gland secretion is a complex process and involves the interaction of many proteins. In acinar cells, following stimulation by neurotransmitters cytosolic levels of calcium increases, which activates ion channels that create an osmotic gradient and drives the movement of water through specific channels. Knockout mice for AQP5, NKCC1, IP3R types 2 and 3, matriptase, and the M3 and M1 muscarinic receptors are all reported to have a decrease in saliva flow [404–408]. The interplay between the epithelia and the immune system adds a further layer of complexity because T-cell knockouts of IP3K, STIM1/STIM2, and ID3 and overexpression of IL-12, BAFF, and sTNFR1 are all also reported to induce loss of gland function and may initiate it by different pathways [335,409–413].

However, in the cases of inflammation within the gland there is increasing evidence for involvement of the epithelial cells [414,415]. Salivary epithelial cells can act as nonprofessional antigen-presenting cells by releasing proinflammatory cytokines, chemokines, and costimulatory molecules that contribute to the inflammatory response [414,416]. A key function of the salivary epithelia is to act as a barrier and loss of tight junction function is linked to the development of chronic immune disease. In addition to allowing the introduction of neoantigens, loss of barrier function could also redistribute apical and basolateral components and disrupt the secretory machinery of the salivary gland [417]. This can be initiated in response to cytokines such as TNF and IFN [418]. Redistribution of proteins important in release of secretory granules could be associated with the misdirected release of

exosomes towards the extracellular matrix rather than the lumen of the gland and contribute to disease progression [419]. However, our understanding of why these changes occur and their mechanism are limited.

Apoptosis of the salivary epithelial cells has been proposed as a major component in the pathogenesis of Sjogren's syndrome [420]. Dysregulated apoptosis in epithelial cells by cytokines is reported to trigger T-cell activation leading to the induction of Sjogren's syndrome associated autoantibodies [421]. Similarly, TLR3 and TLR9 activation are also associated with apoptosis in salivary derived epithelial cells [422,423].

Autophagy is a dynamic cellular process initiated in response to stress induced by hypoxia, starvation, and likely homeostasis and ER stress response in salivary glands [424]. Because of the intense secretory activity in the salivary gland there is likely high levels of ER stress and activation of the unfolded protein response. Autophagy plays a protective role and regulates cell death in cooperation with apoptosis. During autophagy, protein, organelles and cytoplasm become enveloped within double membrane vesicles (*i.e.*, autophagosomes) and are subsequently degraded after fusion with lysosomes, then recycled to maintain cellular metabolism. Failure to complete autophagy induces apoptosis and is associated with accumulating proteins such as phosphorylated α-synuclein (α-syn) and amyloid-β, in diseases such as Alzheimer, Parkinson, and Huntington disease. The autophagy pathway is upregulated in tissue from SS patients [424,425]. In salivary gland cells, autophagy and apoptosis, are proposed to contribute to a redistribution of Ro/SSA and La/SSB to the cell surface and presentation for autoantibody production [426]. However, the mechanism and triggers for activation of these pathways is not clear but may be in response to viral infection which is known to be modulated in epithelial cells in response to virus infection [427]. Viruses such as hepatitis C virus, which is associated with initiating Sjogren's syndrome like symptoms upon infection is reported to increase autophagic flux [428].

While much of the work on salivary gland epithelial cells has focused on the role of the acinar cells there is likely a strong connection between acinar function and ductal integrity. Fluid section is initiated by the acinar cells but this NaCl rich fluid is modified by the ductal cells which is essential for its biologic function. Damaged ducts will likely block the flow of proteins from the gland and could result in damaging the acinar cells by the many digestive enzymes in saliva. A critical ductal protein in this process is the chloride secreting channel cystic fibrosis transmembrane conductance regulator (CFTR). Confocal imaging and western blots of NOD mice show reduced expression of CFTR. Treatment of mice with small molecule drugs that improve the activity or trafficking of CFTR or over expression of CFTR by gene transfer, restored salivary gland activity and decrease inflammation and fibrosis in the tissue. This change in a ductal protein results in changed in acinar cells including calcium signaling and expression of AQP5 [429].

Other ductal proteins that sense increased Ca or ATP as a result of injury are the Purinergic receptors. P2X7R is overexpressed in glands of patients with pSS [430].This has been linked to the release of the proinflammatory cytokine IL-1β and activation of the inflammasome complex. P2X7R stimulation in salivary acinar cells can result in depolarization of the mitochondrial membrane and production of reactive oxygen species and cleavage and release of α-fodrin which maybe an initiating event associated with pSS. Inhibition of P2X7 receptors can reduce the inflammation in the gland and associated exocrinopathy [431].

It is reasonable to assume that self-proteins aberrantly expressed in both SS patients and animal models with SS-like disease represent targets for the immune response and are not merely coincidental observations. Identifying these changes in expression are likely at the center of the altered signalling network and immune imbalance associated with the autoimmunity. One such protein recently studied is bone morphogenic protein-6 (BMP6), first noted to be selectively increased in the salivary glands of patients with SS compared to normal controls in microarray studies. When its expression is increased in the salivary gland cells of C57BL/6 mice, loss of salivary gland function with an increase in infiltrating lymphocytes is noted [432]. In addition to its effect on salivary gland function, increase BMP6 is likely to affect the activity of other cells in the gland, such as infiltrating lymphocytes and bone marrow mesenchymal stem cells [433,434].

In contrast, Protein kinase C-delta expression is reduced in lymphocytes of patients with SS [435], but deletion of this gene in C57BL/6 mice results in lymphocytic infiltration of multiple organs, including the salivary glands, resulting in hyposalivation [436]. Another protein important in T cell receptor signalling is phosphatidylinositol-3- kinase (PI3K) [437]. Deletion of PI3K from T cells of C57BL/6 mice leads to selective loss of lacrimal gland secretory function [409]. Lastly, another molecule important for T cell receptor signalling is the inhibitor of differentiation-3 (Id3) protein. When deleted from C57BL/6 mice, these mice showed loss of both lacrimal gland and salivary gland function in the absence of detectable lymphocyte infiltrations of the glands or production of either anti-Ro or anti-La antibodies [438].

Overall, results from studies co-ordinately performed with SS patients and appropriate mouse models exhibiting SS-like disease not only validate important concepts of SS pathology as an autoimmune process, but also the use of animal models to identify potential molecular and cellular processes currently not possible in human medicine. The various mouse models for SS continue to provide increasing knowledge of issues that were largely missed in studies looking exclusively at SS patients. These include the concepts that (a) loss of salivary and lacrimal gland function may occur before or even without identifiable lymphocytic infiltration of the glands, even though lymphocytes most likely participate in the pathophysiology of the disorder, (b) the innate immune system is important in the pathophysiology of the disease and not simply the result of a disorder in the adaptive immune system in which self-tolerance has been lost, (c) salivary and lacrimal gland injury may occur via multiple different mechanisms that may not be the same in all patients, (d) autoantibodies and B lymphocytes are critical factors in the early stages of development and onset of SS pathophysiology, (e) SS progresses through many stages of disease that apparently occur over a course of many years in patients, a fact supported by molecular and cellular studies in the mouse models, (f) cytokines such as IFN, IL-14, lymphotoxin and IL-17 may be variable at different stages of the disease, thereby regulating the direction of disease onset, (g) despite the fact that SS has been shown to have a strong IFN signature and that there is considerable interest in viruses as an environmental trigger for onset of SS [439,440], this concept remains an open question, and (h) events necessary for the progression of SS through its various stages, including lymphomagenesis, will require further studies in animal models before headway is made in delineating the various subtypes of SS and subsequently understanding what patients within each subtype are undergoing.

5. Initial approach and need for treatment

Sjögren's syndrome is difficult to diagnose and equally challenging to manage. No cure or agent able to induce remission exists. Presently, therapeutic goals are targeted toward symptom palliation, prevention of disease complications (especially in the eyes and mouth) and treatment of serious and/or life-threatening systemic manifestations with immunosuppressive therapy. The treatment algorithm should therefore initially focus on the oral, ocular and systemic morbidities. Choice of therapy depends upon the severity of symptoms, disease severity and the degree of internal organ involvement.

Patient surveys consistently identify sicca symptoms, fatigue, musculoskeletal pain and cognitive dysfunction as the most prevalent and disabling symptoms in SS [41,441]. Two studies examined the impact of severe dry eye disease by utility assessment and documented utility (patient perceived morbidity) values similar to those found in patients with angina and/or on dialysis [442,443]. Additionally, in this

Table 6
Preservative free artificial tears.[a]

Product	Active ingredients	Notes
Bion® Tears (Alcon/Novartis)	0.1% Dextran 70; 0.3% hypromellose 2910	
Blink® PF (Johnson & Johnson)	0.25% PEG 400	
Clear Eyes® Pure Relief (Prestige)	0.25% glycerin	Preservative free multi-dose bottle
FreshKote® Preservative Free (Focus Laboratories)	2.7% polyvinyl alcohol, 2.0% povidone	Preservative free multidose bottle; stored behind pharmacy counter; also contains glycerin
GenTeal® Tears (Alcon/Novartis)	0.1% Dextran 70; 0.3% hypromellose 2910	
NanoTears® TF PF (Altaire)	0.4% PEG; 0.3% PEG	
Oasis® Tears (Oasis Medical)	0.2% glycerin	
Refresh Classic® (Allergan)	1.4% polyvinyl alcohol, 0.6% povidone	
Refresh Optive® (Allergan)	0.5% CMC; 0.9% glycerin	
Refresh Optive Advanced® (Allergan)	0.5% CMC, 1% glycerin, 0.5% polysorbate 80	
Refresh Optive Mega-3® (Allergan)	0.5% CMC, 1% glycerin, 0.5% polysorbate 80	Also contains castor oil and flaxseed
Refresh Optive Sensitive® (Allergan)	0.5% CMC, 0.9% glycerin	
Refresh Plus® (Allergan)	0.5% CMC	
Soothe® PF (Bausch & Lomb)	0.6% PPG, 0.6% glycerin	
Systane® (Alcon/Novartis)	0.4% PEG 400; 0.3% PEG	
Systane Ultra® PF (Alcon/Novartis)	0.4% PEG 400, 0.3% PPG	
Theratears® PF (Akorn)	0.25% CMC	

CMC = carboxymethylcellulose; PEG = polyethylene glycol; PPG = propylene glycol.
[a] Not an exhaustive list.

particular population, undiagnosed and/or untreated xerostomia and keratoconjunctivitis sicca (KCS) frequently result in devastating, costly medical and dental complications including oral and ocular infections, accelerated caries, loss of dentition, corneal ulcers/perforations and visual impairment [444].

In the 1950s, Sjögren's syndrome was once described as "a chronic and relatively benign form of systemic lupus erythematosus" [445]. However, in recent years, physician perceptions regarding the overall morbidity associated with SS have dramatically changed. This awareness is further heightened by the recognition that SS is frequently complicated by the development of non-Hodgkin's B-cell lymphomas [69,446]. A study in Britain noted a much higher percentage of serious internal organ involvement in lupus compared to SS, but also reported that the overall level of functional disability in both disorders was the same [447]. At least 7 studies using various instruments have documented poor quality of life (QOL) (including oral health QOL) in SS versus healthy controls [41,448–453], and QOL that is diminished to the same degree or worse compared to patients with rheumatoid arthritis [448,449] or fibromyalgia [449].

Higher rates of unemployment [451,454] and increased health care costs have also been observed in the SS population. In the United Kingdom direct annual health care costs were found to be similar in individuals with primary Sjögren's syndrome and rheumatoid arthritis but more than twice the annual health care costs of patient controls [455]. Not surprisingly, SS patients have higher levels of caries, more tooth extractions and higher dental (especially out of pocket) expenses over a lifetime compared to the normal population [25,456]. In 2003-4, Sjögren's syndrome-specific language was formally incorporated into the revised U.S. Social Security Administration disability guidelines [457].

In addition to the typical SS-related problems, the clinician also must consider other comorbidities that are highly prevalent in SS and occur more frequently than expected by chance alone. These comorbidities include moderate to severe anxiety (≤ 48%), depression (≤ 47%) and fibromyalgia (≤ 47%) [41,73,74,214,448,457,458]. These additional disorders can exacerbate many SS symptoms such as fatigue, pain, dryness, and cognitive dysfunction and, thereby, add to the overall burden of illness and further complicate SS assessment and management. The patient's psychosocial needs should also be addressed as part of the overall treatment plan.

5.1. Treatment of dry eyes

The correlation between the severity of ocular symptoms and the results of objective tests for dry eyes is often poor [459,460]. Therefore, regardless of symptom severity, every Sjögren's patient should see a cornea or dry eye specialist at least once for a comprehensive evaluation. This should include: 1) measurement of tear production; 2) staining of the cornea with fluorescein and the conjunctiva with lissamine green to assess the degree of ocular surface damage; and 3) inspection of the eyelids for signs of meibomian gland dysfunction (MGD). Although KCS in SS cannot be cured, effective therapies are currently available to manage symptoms and prevent complications. While SS is classically thought to cause decreased tear production or aqueous tear deficient dry eye, there is also evidence that many SS patients have significant MGD, also known as blepharitis, leading to evaporative dry eye as well ([38]. Although KCS is the most frequent ocular manifestation of SS, it is important to note that SS patients are also at risk for other vision-threatening ocular complications such as corneal melts, scleritis, and optic neuritis [31,461].

Recently, Foulks et al, in conjunction with the Sjögren's Syndrome Foundation, Inc. (SSF) published clinical practice guidelines for the management of dry eye associated with SS ([30]. In that algorithm, the treatment of KCS is approached in a step-wise fashion and patients are divided into those with or without MGD. Therapies are subsequently chosen based on the nature and severity (graded 1-4) of the disease and tailored to the individual patient. To varying degrees, many SS patients suffer from both problems.

For patients with aqueous tear deficiency (level 1) modifications of the environment (e.g. avoidance of windy or dry environments) and activities of daily living can be helpful. However, if these measures are inadequate, the first line therapy for dry eye should be lubrication with artificial tears in reusable bottles containing preservatives; these drops are dosed as needed to four times daily.

It is helpful to note that there are important differences between artificial tears with or without preservatives. Preservatives in certain preparations de-stabilize the tear film and can be toxic to the ocular surface, especially if used frequently throughout the day. A general rule-of-thumb is that patients with mild dry eye should not use any supplemental tears with preservatives more than 4 times a day. Sjögren's patients with moderate-to-severe dry eye should be instructed to only use preservative-free artificial tears (Table 6) which typically

Table 7
Higher viscosity artificial tears.[a]

Product	Preservatives?	Active ingredients	Notes
Blink® Gel Tears (AMO)	Yes	0.25% PEG 400	
GenTeal® Moderate Liquid Drops (Alcon/Novartis)	Yes	0.1% Dextran 70; 0.2% glycerin; 0.3% hypromellose	
Lacrisert® (Bausch & Lomb)	No		Prescription-only; dissolvable pellet inserted inside lower eyelid
Oasis® Tears Plus (Oasis Medical)	No	0.2% glycerin	
Refresh Celluvisc® (Allergan)	No	1% CMC	
Refresh Liquigel® (Allergan)	Yes	1% CMC	
Refresh Optive® Gel Drops (Allergan)	Yes	1% CMC; 0.9% glycerin	
Systane® Gel Drops	Yes	0.4% PEG 400; 0.3% PPG	
TheraTears® Nighttime dry eye therapy (Akorn)	No	1% CMC	

CMC = carboxymethylcellulose; PEG = polyethylene glycol; PPG = propylene glycol.
[a] Not an exhaustive list

come in single-use individual vials.

In general, thicker or more viscous artificial tear preparations (Table 7) stay on the ocular surface longer, but also tend to blur vision. Since supplemental tears at best remain on the surface of the eye < 60 minutes, regular use is recommended to optimize treatment results. Additionally, ocular gels or ointments are utilized at bedtime for longer lasting relief (Table 8). Another option for longer lasting relief is the preservative-free hydroxypropyl cellulose insert or Lacrisert® (Bausch & Lomb, Bridgewater, NJ) [462]. This insert is placed inside the lower eyelid by the patient and releases tears onto the ocular surface throughout the day as the pellet dissolves from body heat.

As dry eye worsens to a moderate severity level (level 2-3), patients often require additional therapies, which may include anti-inflammatory drops or oral prescription secretagogues. Topical steroids can be useful for short-term relief of KCS symptoms, although possible complications such as cataract formation, infection, and secondary glaucoma limit their long-term use [463,464]. A short two to three-week course of topical steroids can be considered in select patients with dry eye flares. Topical 0.05% cyclosporine is thought to decrease inflammation by several mechanisms including inhibition of T-lymphocyte activation [465,466]. The recommended treatment dose is 1 drop to each eye twice daily. The most common side effect is stinging upon instillation, which can be alleviated by refrigeration of the product, instillation 5 minutes after adding a drop of artificial tears, or the concurrent use of a topical steroid for the first two weeks [467].

Recently, topical lifitegrast was approved by the FDA for the treatment of dry eye. Lifitegrast decreases inflammation by blocking the interaction of intercellular adhesion molecule ICAM-1 and lymphocyte function associated antigen LFA-1. In four large, multi-center, randomized clinical trials, lifitegrast was shown to be effective in improving the signs and symptoms of dry eye [468]. Side effects include transient ocular irritation and dysgeusia. Further studies are needed to explore the effectiveness of combination therapy such as the concomitant use of topical cyclosporine and topical lifitegrast. Although not FDA approved for this indication, there is also some evidence that oral secretagogues, such as pilocarpine and cevimeline, may be effective in alleviating dry eye symptoms as well [469–471].

The use of oral omega 3 essential fatty acid supplements is also mentioned in the treatment algorithm. However, a recent large, double-blind, placebo-controlled, multi-center, randomized clinical trial found no benefit over placebo when using these supplements for the treatment of dry eye [472]. Once inflammation of the ocular surface is controlled, punctal occlusion of the openings to the tear ducts (puncta) using plugs or cautery can be helpful in conserving tears [473].

Finally, for patients with severe (level 4) ocular surface disease, additional therapies include the use of topical autologous serum drops [474,475], partial closure of the interpalpebral fissure to reduce evaporation from the ocular surface, or large-diameter scleral contact lenses [476]. Patients with filaments or mucus strands on the surface of the cornea (i.e. filamentary keratitis) may benefit from topical N-acetylcysteine drops, which can be obtained from a compounding pharmacy. In the worst-case scenario, patients with severe (level 4) KCS may also require systemic anti-inflammatory or immunosuppressive medications to control their ocular disease.

For patients with MGD, the first-line treatment requires daily attention to eyelid hygiene with the use of warm compresses, eyelid massage and scrubs. Warm compresses that utilize moist heat, such as a washcloth with warm tap water are preferred. A typical recommendation is to perform warm compresses twice a day with gentle lid massage to encourage flow from the meibomian glands.

In MGD, dryness develops because altered or diminished meibum secretion causes dysfunction of the outer oily layer of the tear film and predisposes to increased tear evaporation from the ocular surface. A variety of lipid containing tears have been developed (Table 9) to address this problem and may be used in addition to other tear substitutes. Additional measures for mild-moderate (level 2-3) MGD include the use

Table 8
Gels and artificial tear ointments.[a]

Formulation	Product	Active ingredients
Gels		
	GenTeal® Gel (Novartis)	0.3% hypromellose
	Liposic® (Bausch & Lomb)	carbomer
	Systane® Lubricant Eye Gel (Alcon/Novartis)	0.3% hypromellose
Ointments		
	GenTeal® Nighttime Ointment (Alcon/Novartis)	3% mineral oil; 94% white petrolatum
	Refresh Lacrilube® (Allergan)	42.5% mineral oil; 56.8% white petrolatum
	Refresh PM® (Allergan)	42.5% mineral oil; 57.3% white petrolatum
	Retaine PM® (OcuSoft)	20% mineral oil 80% white petrolatum
	Soothe® Night Time Ointment (Bausch & Lomb)	20% mineral oil; 80% white petrolatum
	Systane® Nighttime Ointment (Alcon/Novartis)	3% mineral oil; 94% white petrolatum

[a] Not an exhaustive list.

Table 9
Lipid-based artificial tears.

Product	Preservatives?	Active ingredients
Refresh Optive Advanced® (Allergan)	No	1% glycerin, 0.5% CMC, 0.5% polysorbate 80
Retaine MGD® (OcuSoft)	No	0.5% light mineral oil, 0.5% mineral oil
Soothe XP® (Bausch & Lomb)	Yes	1% light mineral oil, 4.5% mineral oil
Systane Balance® (Alcon/Novartis)	Yes	0.6% PPG, mineral oil
Systane Complete® (Alcon/Novartis)	Yes	0.6% PPG; mineral oil
Tears Again® (OcuSoft)	Yes	Liposomal soy lecithin, vitamin A palmitate, vitamin E

of topical antibiotics, such as erythromycin 0.5% ophthalmic ointment or azithromycin drops, as well as oral antibiotics such as doxycycline [30]. Patients with refractory MGD may be candidates for new treatments such as meibomian gland probing, intense pulsed light treatment, or continuous controlled thermal compression (Lipiflow System®). However, these treatments are often not covered by insurance and must be paid for out-of-pocket. Some of the other recommendations outlined above for the treatment of aqueous tear deficiency are also applicable to patients with MGD.

5.2. Treatment of oral manifestations

Oropharyngeal dryness related to salivary dysfunction is an almost universal manifestation of SS and often severe enough to cause significant QOL impairment. It may also cause difficulty with eating and nutrition, dental complications, recurrent oral candidiasis and recurrent salivary gland swelling.

In all patients with xerostomia, it is important to identify and mitigate potential aggravating factors. Medications known to cause dry mouth [292,477] should be discontinued or substituted whenever possible. Common offenders include anti-muscarinics, antidepressants (especially tricyclics), anti-psychotics, antihistamines, diuretics, and beta blockers. Lifestyle modifications can also be useful. Eating smaller, more frequent meals can help stimulate salivary flow. To maintain oral comfort, patients should take frequent, small sips of water or non-carbonated sugar-free drinks (except citrus juices) throughout the day. Patients should be encouraged to avoid low humidity conditions (such as air-conditioned environments during summer months) and use a humidifier in the bedroom, especially during the fall and winter months. Avoiding the use of mouthwashes and rinses that contain alcohol or witch hazel is important as these can aggravate dryness and sometimes cause burning. Mouth breathing will typically exacerbate nocturnal symptoms and can sometimes be corrected with proper otorhinolaryngologic care.

There are two approaches to xerostomia treatment in SS: saliva replacement and stimulation of salivary flow with secretagogues. A variety of over-the-counter (OTC) artificial saliva products (Table 10) can provide short term relief, but require continual use (e.g. 1-2 squirts every hour while awake) for maximal benefit. Therefore, OTC saliva substitutes are best utilized in provocative circumstances such as air travel, in place of water to alleviate nocturnal fluid ingestion, or as adjunctive treatments to other therapies. Two prescription saliva substitute powders (SalivaMAX™, NeutraSal™) are also FDA approved for dry mouth. The powders are dissolved in water to create a supersaturated calcium phosphate solution that is used as a gargle several times per day. These rinses have been studied in the oncology population and may alleviate mucositis as well as xerostomia [478]. Patients should be counseled not to eat or drink within 15 minutes of use. Additionally, moisturizing gels and oral lubricants, such as topical vitamin E oil or mineral oil, can also be applied to the tongue and inner cheeks after meals and at night to soothe the mouth.

For patients with mild symptoms, any gustatory or masticatory stimulus can be used as a secretagogue to stimulate flow. A variety of sugar-free lozenges, candies and gums are available to serve this purpose (Table 11). Among OTC products, there is evidence that green tea lozenges (MightTeaFlow®) may actually stimulate salivary flow better than a placebo [479]. The use of xylitol containing products is particularly encouraged as this agent is superior to other artificial sweeteners for caries prevention [480].

Systemic therapy with prescription secretagogues (pilocarpine, cevimeline) should be considered in any patient with significant symptoms, a history of oral complications, or at risk for oral complications due to an abnormally low whole mouth salivary flow rate (< 0.3 ml/min). Therapeutic success depends on residual salivary gland function as reflected by results of sialometry or salivary scintigraphy. In placebo-controlled clinical trials pilocarpine at 20-30 mg daily in divided doses was shown to significantly improve xerostomia, salivary flow, and other oral symptoms as well [470,481]. Major side effects included sweating and flushing. Cevimeline up to 90 mg/day in divided doses has shown similar benefits [482,483]. Although pilocarpine and cevimeline are only FDA approved for the treatment of xerostomia associated with Sjögren's syndrome, the available evidence suggests that these secretagogues may help other sicca symptoms as well [469–471,481–483] especially when regularly used at the maximum therapeutic doses. Both medications are best tolerated when starting with a low dose after meals and advancing slowly on a weekly basis to alleviate side effects until the target dose is achieved. Long-acting guaifenesin, an expectorant, at doses of 600 mg to 1200 mg by mouth twice daily seems to stimulate increased secretions in the respiratory tract and can be useful to treat dry nose, dry throat and dry lungs.

There are also two devices (Salitron™, Saliwell™) FDA approved in 1990 and 2017, respectively, that utilize electrical stimulation locally of the salivary glands to increase salivary secretion [484,485]. The Salitron™ system involves a handheld probe that is placed on the dorsal tongue for 5 minutes three times daily; this device is no longer being manufactured but is still in use. The Saliwell GenNarino™ has components embedded into a removable mouthguard that can be controlled with a remote. The Saliwell Crown™ involves permanent implantation of a miniature electro-stimulating device near the third molar. Although these devices cause no cholinergic side effects, their routine use has been hampered by cost and insurance limitations.

Meticulous dental hygiene is also critical to alleviate the risk of dental complications, such as cracked teeth, loose fillings, accelerated caries and loss of dentition. Use of an electric toothbrush, regular flossing, and mouth rinsing with water after meals should be encouraged. All patients with SS should see a dentist or oral medicine specialist every 3 to 6 months to help with the early diagnosis and treatment of dental caries. The 2017 SSF Clinical Practice Guidelines for oral management recommend application of topical fluoride in any form for all SS patients with dry mouth [233]. For example, one strategy would be to brush 1.1% neutral NaF gel on the teeth after regular nighttime brushing at bedtime, leave on for 30 minutes, floss and then rinse or swallow. Chlorhexidine varnish, gel, or rinses, as well as non-fluoride re-mineralizing agents (e.g. MI Paste®) can be also considered as adjunctive therapies in patients with severe caries. Finally, based on clinical experience and results in animal studies [486,487] efforts to increase salivary production through pharmacological measures are also mentioned in the guidelines and potentially useful for caries prophylaxis as well.

Oral yeast infections are a common complication of severe

Table 10
Artificial salivas and oral lubricants for dry mouth.[a]

Product	Formulation	Ingredients	Manufacturer/Distributor
[b]Aquaoral™	Spray	Oxidized glycerol triesters (TGO), silicon dioxide, aspartame, and artificial flavoring	Mission Pharmacal Company, San Antonio, TX
Biotene®	Spray	Purified water, glycerin, xylitol, PEG-60, hydrogenated castor oil, VP/PA copolymer, flavor, sodium benzoate, xanthan gum, methylparaben, propylparaben, sodium saccharin, cetylpyridinium chloride	GlaxoSmithKline Consumer Healthcare, L.P., Pittsburgh, PA
	Gel	Glycerin, water, sorbitol, xylitol, carbomer, hydroxyethyl cellulose, sodium hydroxide	
Entertainer's Secret™	Spray	Sodium carboxylmethylcellulose, potassium chloride, dibasic sodium phosphate, parabens, aloe vera gel, glycerin	KLI Corporation, Carmel, IN
GC Dry Mouth	Gel	Polyglycerol, pure water, sodium carboxymethylcellulose, carrageenan, sodium citrate, flavors, ethyl p-hydroxybenzoate	GC America, Inc, Alsip, IL
MEDActive® Patient-Friendly™	Gel Spray	Water, glycerin, xylitol, poloxamer 407, dimethicone, EDTA, flavor, potassium sorbate, sodium saccharin, sucralose, xanthan gum	MEDActive Oral Pharmaceuticals, LLC, Odessa, FL
Moi-Stir®	Spray	Water, glycerin, sodium carboxymethycellulose, methylparaben, potassium chloride, dibasic sodium phosphate, propylparaben, calcium chloride, sodium chloride, magnesium chloride, flavors	Kingswood Laboratories, Inc, Indianapolis, IN
MouthKote®	Spray	Water, xylitol, sorbitol, Yerba Santa, citric acid, natural lemon-lime flavor, ascorbic acid, sodium benzoate, sodim saccharin	Parnell Pharmaceuticals, Inc. San Rafael, CA
[b]NeutraSal®	Rinse	Dibasic sodium phosphate, monobasic sodium phosphate, calcium glycerophosphate, sodium chloride, sodium bicarbonate, silicon dioxide	Invado Pharmaceuticals, LLC, Pomona, NY
Oasis®	Spray	Lemon oil, ethyl cellulose polymer, zanthan gum, xylitol, sucralose, eucalyptus oil, wintergreen oil, sodium bicarbonate, glycerol, zinc gluconate, thymol, calcium sulfate, potassium phosphate dibasic	Oasis Consumer Healthcare, Cleveland, OH
OraCoat XyliMelts®	Dissolvable disc	Xylitol, acacia gum, mild natural mint, cellulose gum, calcium carbonate, magnesium stearate	OraHealth, Bellevue, WA
Spry®	Spray	Purified water, xylitol, aloe vera, vegetable glycerin, spearmint flavor, calcium glycerophosphate, cellulose gum, grapefruit seed extract	Xlear Inc, American Fork, UT
[b]SalivaMAX®	Rinse	Dibasic sodium phosphate rinse	Forward Science, Stafford, TX
MightTeaFlow®	Spray	Deionized water, glycerin, xylitol, aloe vera leaf juice, jaborandi leaf extract, xanthan gum, green tea extract, raspberry extract, resveratrol, vitamin D, ascorbic acid, zinc gluconate, calcium bicarbonate, sodium fluoride, sodium bicarbonate, potassium sorbate	Camellix, LLC, Augusta, GA
	Rinse	Deionized water, glycerin, xylitol, aloe vera leaf juice, jaborandi leaf extract, green tea extract, raspberry extract, resveratrol, vitamin D, ascorbic acid, zinc gluconate, calcium bicarbonate, sodium fluoride, disodium phosphate, sodium benzoate	

[a] Not an exhaustive list, adapted from the Sjogren's Syndrome Foundation Product Directory.
[b] Prescription required.

xerostomia in SS, with a prevalence of 74% found in one study [488]. Chronic erythematous candidiasis, with physical exam findings of atrophy of the filiform papillae, mucosal erythema, and/or angular cheilitis is typically seen, as opposed to classical thrush. Patients may complain of glossodynia, stomatopyrosis or intolerance to spicy foods. Prolonged treatment with systemic antifungals is often required (e.g. fluconazole 100-200mg by mouth daily for 3 weeks). Local treatment with clotrimazole lozenges or troches with small sips of water (e.g. 10 mg 5x/day) for 3 weeks work better for patients with minimal salivary flow. Topical clotrimazole cream can be used in conjunction with the above therapies to treat angular cheilitis. The use of secretagogues can be useful in preventing recurrence [489].

About a third of SS patients will develop parotid or submandibular gland swelling over the course of the disease. Proper treatment first requires accurate diagnosis with imaging by CT or MRI and, sometimes a major salivary gland biopsy. In patients with confirmed Sjögren's syndrome, the differential diagnosis includes bacterial sialadenitis, sialolithiasis, sialostenosis, inflammatory sialadenitis, sialadenosis, non-Hodgkin's B-cell lymphoma (usually MALT) lymphoma, or other tumors.

Table 11
Non-systemic oral secretagogues.[a]

MEDActive® Patient-Friendly™	Lozenges	Water, glycerin, xylitol, poloxamer 407, dimethicone, EDTA, flavor, potassium sorbate, sodium saccharin, sucralose, xanthan gum	MEDActive Oral Pharmaceuticals, LLC, Odessa, FL
MightTeaFlow®	Lozenges	Xylitol, sorbitol, natural flavors, green tea leaf extract, jaborandi leaf extract, acacia gum, silicon dioxide, magnesium stearate, sucralose	Camellix, LLC, Augusta, GA
	Gum	Xylitol, maltitol, gum base, natural and artificial flavors, glycerine, gum arabic, camellia sinensis (green tea) leaf extract, artificial color, sucralose, jaborandi leaf extract, resinous glaze, carnauba wax, and BHT (to maintain freshness)	
OraMoist™	Time-Released Patch	Xylitol, polyvinylpyrrolidone, carbomer homopolymer type A, lemon flavor, citric acid, calcium carbonate, hydroxypropyl cellulose, triglyceride, sodium chloride, silicone dioxide, magnesium stearate, annatto, glucose oxidase, lysozyme, lactoferrin	Quantum Health, Eugene, OR
Salese™	Lozenges	Lemon oil, eucalyptus oil, wintergreen oil, thymol, xylitol, zinc gluconate, sodium bicarbonate, calcium sulfate, potassium phosphate, xanthan gum	Nuvora, Santa Clara, CA
SalivaSure™	Lozenges	Xylitol, malic (apple) acid, dibasic calcium phosphate, sodium citrate dihydrate, stearate acid, citric acid, magnesium stearate, silica colloidal, sodium carboxy methyl cellulose	Scandinavian Formulas, Inc, Sellersville, PA
Spry™	Gum	Xylitol, gum base, natural spearmint oil, gum arabic, calcium carbonate, vegetable glycerin, soy lecithin, carnauba wax	Xlear Inc, American Fork, UT
XyliChew™	Gum	Xylitol, gum base, vegetable glycerin, natural fruit flavors, gum arabic, sunflower lecithin, and carnauba wax	Nature's Stance, Poway, CA

[a] Not an exhaustive list, adapted from the Sjogren's Syndrome Foundation Product Directory.

Acute episodes of unilateral glandular swelling associated with facial redness and/or fevers suggest bacterial sialadenitis until proven otherwise. An attempt should be made to culture secretions at the orifice of Stenson's or Wharton's duct after milking the salivary gland. A recent systematic review recommended treatment with cephalosporins or fluoroquinolones to cover *Staphyloccous aureus*, *Viridans streptococci*, and, less commonly, gram-negatives [490]; metronidazole would be added in rare situations when anaerobes are suspected. Episodic unilateral glandular swelling, particularly, after chewing or eating is often due to sialolithiasis or sialostenosis with ductal obstruction due to mucus plugs. These episodes can usually be managed supportively with pain control, hot compresses, milking of the affected gland, and sucking on sour candies. Patients are sometimes aware of passing gravel or sour tasting mucus in the mouth when the swelling starts to subside. Recurrences can be prevented by regular milking of the salivary glands and the use of systemic secretagogues. In cases of persistent duct obstruction, intervention with sialoendoscopy may be indicated. Intermittent unilateral or bilateral salivary glandular (usually parotid) enlargement that lasts for days may occur in SS due to inflammatory sialadenitis. Acute cases can be treated with a prednisone taper. Chronic cases can be treated with hydroxychloroquine or low-dose methotrexate [491]. In the case of sialadenosis, tapering of corticosteroids, if applicable, should be pursued and patients should be counseled on weight loss and screened for hyperlipidemia. Asymmetrical glandular enlargement, especially if nodular or hard, or persistent swelling greater than 12 weeks in duration that is not responsive to treatment, should raise concern for possible neoplasm. A biopsy may be indicated to help confirm the diagnosis, particularly if there is concern about lymphoma.

5.3. Treatment of systemic manifestations

5.3.1. Practice guidelines development

As alluded to earlier, the first ever US clinical practice guidelines (CPG) for management of the ocular, oral and rheumatologic/systemic manifestations of SS were developed under the auspices of the Sjögren's Syndrome Foundation, Inc. and published beginning in 2015 [30,492]. All working groups followed a highly rigorous process with guidance from major professional societies including the Institute of Medicine, American Academy of Ophthalmology, American Dental Association and the American College of Rheumatology. The principles of AGREE and GRADE methodology were utilized to construct evidence-based guidelines and/or CPG based on expert opinion when evidence was insufficient. A modified Delphi process was used to achieve consensus among a multidisciplinary panel of experts and key stake holders before the CPG were adopted. This process is ongoing, and guidelines will be expanded and/or revised as new information becomes available.

The initial rheumatology CPG focused on treatment of inflammatory musculoskeletal pain, fatigue and the use of biological therapy in SS. In the next 3 years, guidelines are planned for interstitial lung disease, vasculitis, renal disease, central nervous system manifestations, peripheral neuropathies and non-Hodgkin's B-cell lymphomas. Presently, however, standards of care for these other problems vary widely among different centers and clinical decisions are based on uncontrolled studies, small case series/reports or experience in treating similar problems in other closely related disorders such as systemic lupus erythematosus and rheumatoid arthritis.

5.3.2. Inflammatory musculoskeletal pain

Arthralgias and myalgias are highly prevalent among individuals with SS, and in some SS patient groups, inflammatory polyarthritis has been observed in 15-33% [66,67]. The recently published rheumatology CPG for treatment of inflammatory rheumatic pain [60] recommended the use of DMARDS in a step-wise approach with hydroxychloroquine as first line therapy followed by the initiation of methotrexate (either alone or in addition to hydroxychloroquine). Low dose (< 15 mg daily) short-term (< 1 month) corticosteroids can be utilized as bridge therapy while trying to find a steroid sparing agent. Leflunomide, sulfasalazine and azathioprine were deemed to have similar efficacy as steroid sparing agents except in situations with evidence of other major organ involvement (e.g. interstitial lung disease) where azathioprine is preferred to treat multi-system disease. Use of cyclosporine to treat joint pain in SS was also mentioned. Treatment with higher doses of corticosteroids or for longer periods of time should only be considered as the worst-case scenario for patients who have failed multiple DMARDS with frequent attempts to taper as soon as possible while searching for alternative therapies. The CPG on the use of biological therapy in SS also mentioned the possibility of using TNF-α inhibitors for Sjögren's patients who exhibit overlapping features with rheumatoid arthritis and/or the use of intravenous rituximab for patients with severe or treatment refractory extra-glandular manifestations including inflammatory polyarthritis.

5.3.3. Treatment of fatigue

Patients with SS can have disabling fatigue, and, in fact, fatigue was shown to be the predominant predictor of poor general health and physical function in a 2009 cohort study that compared SS patients to age and sex matched peer controls [41]. The mainstay of treatment for fatigue in SS is participation in regular low-impact aerobic exercise and self-care measures [60]. This approach has proven successful in several patient groups including those with lupus [493–495], rheumatoid arthritis [496], multiple sclerosis [497] and SS [498]. The CPG working group also suggested the use of hydroxychloroquine in selected cases to treat fatigue despite lack of evidence from controlled trials. Additionally, the evaluation and treatment of co-morbidities that cause fatigue in SS such as sleep disorders (e.g. obstructive sleep apnea), depression, fibromyalgia, hypothyroidism, vitamin D deficiency, vitamin B12 deficiency, metabolic disorders and anemia should also be pursued.

5.3.4. Treatment of renal manifestations

The most common renal manifestation of SS is chronic tubulointerstitial nephritis. If there is evidence of severe or active interstitial nephritis, treatment with high dose systemic corticosteroids (prednisone 1 mg/kg/day up to 60 mg per day and then tapering) is reasonable [499]. If a steroid sparing agent is required due to disease relapse upon steroid withdrawal, azathioprine [499] or mycophenolate mofetil [500] have been used with success. Renal tubular acidosis (RTA), especially Type I distal RTA, also occur in SS and are treated with alkali to correct the acidemia and, when necessary, potassium for persistent hypokalemia. Glomerular involvement (e.g. membranoproliferative glomerulonephritis) is relatively uncommon and should raise suspicion for concomitant SLE or cryoglobulinemic vasculitis. The treatment algorithms used for glomerulonephritis associated with lupus or vasculitis should be followed.

5.3.5. Treatment of interstitial lung disease

Patients with Sjögren's syndrome can develop non-specific interstitial pneumonitis (NSIP), usual interstitial pneumonia (UIP), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), and less commonly primary pulmonary lymphoma of the BALT (bronchial associated lymphoid tissue) variety. Follicular bronchiolitis can be also be present, often co-existent with interstitial lung disease (ILD). The treatment of ILD in SS depends on the severity of symptoms and effects on lung function. The course can be highly variable ranging from spontaneous improvement and/or stabilization to progression and death [501,502].

In asymptomatic or minimally symptomatic patients with imaging findings of interstitial lung disease but without significant abnormalities on pulmonary function tests, patients can be monitored closely in lieu of starting active treatment. Monitoring may include repeat high-resolution CT scans and pulmonary function testing every 6 to 12

months. For symptomatic patients, or those with worsening pulmonary function over time, regardless of the pattern of involvement, treatment with oral corticosteroids (e.g. prednisone 0.5–1 mg/kg/day) should be considered as first line therapy. Although there is no robust evidence to support this approach in SS, anecdotal reports from small case series suggest benefit with stabilization of NSIP, COP, and LIP [502]. Among individuals with the idiopathic interstitial pneumonias, UIP patients have the worst prognosis and are least responsive to treatment; however, in SS this is not always the case [503]. When SS patients fail first line therapy, escalation of treatment with other immunosuppressive therapy is recommended. There is limited data that support the use of azathioprine or mycophenolate mofetil as steroid sparing agents, extrapolated from small case series showing efficacy for ILD in SS and other connective tissue diseases [504,505]. More recently, a 2012 registry study from France reported improvement in 6 of 8 patients with SS-related ILD (patterns not specified) following treatment with intravenous rituximab [506]. Moreover, the use of rituximab as a steroid sparing agent for Sjögren's "pulmonary disease" was also endorsed in the SSF clinical practice guidelines on the use of biological therapy in SS [60]. Cyclophosphamide combined with prednisone was successfully used in one study of 14 SS patients with biopsy proven lung involvement (NSIP, COP, mixed patterns, follicular bronchiolitis) and may also be considered in treatment refractory cases [507].

5.3.6. Peripheral nervous system involvement

The most common peripheral nervous system (PNS) manifestations of SS are small fiber sensory neuropathy and axonal sensory or sensorimotor polyneuropathy, and occur as part of a much larger spectrum of PNS abnormalities that also includes sensory ataxic neuronopathy (sensory ganglionopathy), mononeuropathy multiplex, cranial neuropathies, autonomic neuropathies and radiculopathies [188,189]. Treatment strategies depend on neuropathy type, severity of symptoms, rate of progression and effect on the overall functioning of the patient. The current standard of care is based entirely on retrospective case series/reports, registry studies and expert opinion.

Small fiber sensory peripheral neuropathy in SS can cause dysesthesias and allodynia in a length dependent and/or non-length dependent distribution. The first line treatment is aimed at symptom management, using medications for neuropathic pain such as gabapentin, pregabalin, or serotonin-norepinephrine reuptake inhibitors [508]. Tricyclic antidepressants, although helpful, should generally be avoided as they are likely to exacerbate sicca symptoms. Intravenous immunoglobulin (IVIG) at a dose of 400 mg/kg/day over 5 days, as reported in small case series, may provide additional relief to patients with progressive or refractory symptoms [509–511].

Sjögren's may also cause a rare but disabling sensory ataxic neuronopathy related to "dorsal root ganglionitis" that causes loss of kinesthesia, proprioception and progressive difficulty with ambulation and fine motor movements. Case series suggest benefit from corticosteroids and IVIG, as well as treatment with mycophenolate mofetil 2 g/day [194,511,512].

Axonal sensory and sensorimotor neuropathies affect large nerve fibers and cause paresthesia in the distal extremities in a symmetrical distribution with or without muscle weakness. Patients with mild sensory symptoms are treated symptomatically like those with small-fiber neuropathies. Intravenous immunoglobulin as dosed above should be considered in patients with significant motor deficits or refractory and/or progressive symptoms [511].

Vasculitic neuropathies occur in SS and typically present as mononeuropathy multiplex or as painful asymmetric peripheral neuropathies; they frequently occur in association with cryoglobulinemia. Patients may experience the acute or subacute onset of limb pain associated with paresthesias, dysesthesias and varying degrees of weakness including wrist drop or foot drop. The evaluation should include an assessment for vasculitis in other organs and exclusion of other causes. Treatment should be initiated rapidly with high dose IV and oral corticosteroids (e.g. 1 mg/kg/day) followed by the addition of a steroid sparing agent (e.g. cyclophosphamide oral or IV) [191,195]. Azathioprine and methotrexate may be use as maintenance therapy or in patients who develop toxicity with cyclophosphamide [195,196]. Although not useful for most SS-related neuropathies, IV rituximab showed benefit in 11 of 17 patients enrolled in a prospective cohort registry study in France [513]. Promising results were observed in SS patients with cryoglobulinemia, vasculitis or both and, the SSF CPG on use of biologics in SS also mention this therapeutic option [60].

5.3.7. Treatment of central nervous system manifestations

Central nervous system (CNS) involvement in SS is relatively uncommon but can be devastating. Patterns may be diffuse (e.g. seizures), focal or multifocal [188,189,191]. Clinical presentations can mimic ischemic strokes, or the relapsing-remitting or primary progressive forms of multiple sclerosis. Other causes of similar symptoms must always be excluded. A diagnostic and treatment algorithm similar to that used for systemic lupus is most frequently followed. Depending on symptom acuity and severity, treatments may include IV pulse corticosteroids for 3- 5 days, prednisone at 1 mg/kg/day with a slow taper, azathioprine 1-2.5 mg/kg/day and oral or IV pulse cyclophosphamide.

Neuromyelitis optica (NMO) and its limited form, "NMO spectrum disorder", both occur in SS and cause demyelinating disease in association with anti-aquaporin-4 (anti-NMO IgG) antibodies in the blood [51]. In these instances, treatment algorithms as per current guidelines for idiopathic NMO are followed [201]. Initial therapy includes IV pulse corticosteroids for 5 days followed by a steroid taper and/or therapeutic plasma exchange. This is followed by the use of IV rituximab, azathioprine, or mycophenolate mofetil as steroid-sparing agents for maintenance therapy [514–516]. At the present time, however, it remains unclear whether the prognosis of NMO in SS differs from that of the idiopathic form and whether or not the approach to treatment should change when both disorders coexist.

5.3.8. Treatment of anxiety and depression

Sjögren's patients significantly benefit from treatment of concomitant anxiety and/or depression since these comorbidities not only exacerbate common SS symptoms but also heighten patients' illness perceptions [517]. Many patients look well despite having a chronic autoimmune rheumatic disease and are therefore reluctant to voice their symptoms. They often receive little support from their spouses or families. Therefore, extensive education of patients and families on SS disease manifestations and treatments will often significantly reduce the psychosocial burden of living with a chronic illness. Acknowledgment of the severity of SS symptoms by family members and other healthcare providers is essential in order to enable Sjögren's sufferers to accept their disease and move on. Every individual should be encouraged to join the Sjögren's Syndrome Foundation, Inc. (www.sjogrens.org) or one of its local support groups in order to gain better access to reliable health information, expand their support networks and take advantage of volunteer opportunities to "fight back" against their illness. The overreaching goal of treatment should be to gradually change the patient focus from illness to wellness.

For SS patients who require more aggressive treatment, a non-pharmacologic approach is always preferred. Helpful measures may include counseling, cognitive–behavioral therapy, relaxation techniques, regular exercise, increased exposure to sunlight, treatment of insomnia or guided self-help programs [517,518]. For patients with treatment refractory anxiety and/or depression, psychiatric consultation is necessary to optimize care. Psychoactive drugs with anticholinergic side effects (e.g. alprazolam, amitriptyline) are best avoided to prevent exacerbation of sicca symptoms. Medication choice should also be considered in the context of other comorbidities (e.g. fibromyalgia/chronic pain, insomnia). Patients should be treated with the lowest possible dose of psychotropic medication that will achieve the desired therapeutic effect.

5.3.9. Cognitive dysfunction

SS sufferers frequently complain of "brain fog", a form of cognitive dysfunction characterized by short term memory loss, difficulty with focus and concentration and lack of mental clarity; this may interfere with normal activities and add to the overall disease burden [204,209,441]. Treatment varies by cause. Vitamin B-12 deficiency and hypothyroidism can be easily corrected. All patients benefit from general treatment measures including institution of an aerobic exercise program (if medically permissible), improvement of sleep and treatment of chronic pain. All centrally acting medications (e.g. gabapentin) should be discontinued or substituted, if possible. Patients should be screened for anxiety and depression, and treated as above.

Cognitive remediation therapy has been successfully used to improve cognitive function in other groups with similar problems [519,520] and is now being employed in SS as a complementary treatment to other measures. Training is individualized to help patients better deal with everyday situations and achieve greater autonomy in their social and/or professional lives. Depending on the deficit, training can be utilized to restore deficient functions and/or develop novel strategies to process and organize information and tasks.

Individuals with persistent and/or progressive cognitive dysfunction should undergo formal neuropsychological testing. Frank dementia may occur in SS, albeit rarely [204]. Patients with multiple domains below the fifth percentile on testing or who demonstrate other neurological signs and symptoms associated with cognitive dysfunction require a more thorough evaluation for possible central nervous system SS, a manifestation that requires different therapy.

5.4. Perioperative management

Every SS patient who is planning to have elective surgery under general anesthesia should meet with their rheumatologist about 3-4 weeks ahead of time in order to make the necessary preparations for perioperative care [521,522].

5.4.1. Patient instructions

All oils (e.g. vitamin E oil, fish oils, flaxseed oil) used for management of dry eyes and dry mouth as well as low-dose aspirin used for Raynaud's should be discontinued 2 weeks preoperatively in order to minimize bleeding risk. Copious amounts of artificial saliva, sugar-free lozenges and preservative-free artificial tears can be utilized as temporary substitute therapies. Individuals on chronic steroids should undergo a fasting cortisol to determine the need for stress glucocorticoids perioperatively. Ideally, corticosteroids in patients who are not adrenally insufficient should be discontinued or tapered to the lowest possible therapeutic dose preoperatively since the risk of postoperative infection in this patient subset is significantly increased [523–526]. Patients should be counseled that most of their usual Sjögren's prescription and OTC treatments (e.g. pilocarpine tablets, cevimeline capsules, artificial tears, ocular lubricants, artificial saliva, etc.) will likely be non-formulary and unavailable. Therefore, they should bring these items to the hospital along with a schedule for routine administration and, request that their own SS-related medications be administered to them on a regular schedule in the postoperative period.

Current recommendations from the American College of Rheumatology and Association of Hip and Knee Surgeons permit the continuation of certain immunomodulatory or immunosuppressive therapies in the preoperative and postoperative periods [527]. These include hydroxychloroquine, methotrexate, sulfasalazine and leflunomide.

Management decisions on continuation of stronger immunosuppressive therapies including azathioprine, mycophenolate, cyclosporine, tofacitinib and tacrolimus must be made on a case-by-case basis following consideration of the procedure risk versus risk of disease flare and internal organ damage off therapy. In general, in patients with severe disease and high risk of flares with medication interruptions, therapy should be continued, especially in the case of low risk elective procedures. Conversely, in patients with less severe disease manifestations at low risk for flares off immunosuppressive, it is reasonable to briefly interrupt treatment in the perioperative setting, as long as this does not necessitate an increase in glucocorticoid use. Immunosuppressants can be held at least 1 week before surgery and resumed 2 weeks later barring any unforeseen complications [527]. Biological therapies should be held at least one dosing interval before elective surgery and are resumed 2 weeks later as well [527].

5.4.2. Provider instructions

In addition to risks of adrenal insufficiency related to chronic steroid use, providers should also consider the risks of mucosal and dental damage in the perioperative setting. Whenever possible, the use of anticholinergic medications should be avoided. For patients with severe Raynaud's and digital ischemia, non-operative areas can be covered with blankets, operating room temperature increased, and intravenous solutions warmed to help protect against flares. To prevent corneal erosions the eyes should be taped shut intraoperatively with an ocular lubricant or gel. A humidifier should be added to the oxygen rebreathing system to prevent further dryness. For SS patients with caries and/or broken teeth, a mouth guard is required during oro-endotracheal intubation to prevent further dental damage. Likewise, extra lubricants should be used during intubation to protect dry friable mucosa.

In the postoperative period the nurse may need to crush or cut oral medications for SS patients with severe dryness who may also have dysphagia. Ideally, whenever possible, the patient should be positioned upright before administration of oral medications and given a full glass of water to drink. Dry foods such as crackers which are frequently given to patients in the postoperative period should be avoided. The patient's regular routine for treatment of dry eyes and dry mouth should be resumed as soon as possible after surgery.

5.4.3. Conclusions

In summary, the management of Sjögren's syndrome presents the clinician with numerous complex challenges. A comprehensive assessment by experienced providers is necessary to determine the level of morbidity associated with the ocular, oral and systemic manifestations of SS. Treatment algorithms are influenced by disease and symptom severity as well as the degree of internal organ involvement. Clinical practice guidelines are now available for management of keratoconjunctivitis sicca, meibomian gland dysfunction, caries prophylaxis, treatment of fatigue and inflammatory musculoskeletal pain as well as the use of biological therapy in SS. The patient's psychosocial needs should also be addressed in order to optimize care.

6. Research and future treatment considerations

As outlined in this review, many areas of research are ongoing in SS. Basic studies are evaluating the role of the innate and adaptive immune systems as well as various non-immunological cell types in disease initiation and progression. More attention is paid to the various stages of disease that can evolve in patients with SS. Genetic studies are helping to elucidate key players in disease pathophysiology. The contribution of disorders of both aerobic and anaerobic metabolism are being investigated, as they are in other autoimmune diseases, such as SLE [128,528–533]. As these research areas progress, new forms of therapy are conceptualized and investigated in clinical studies. Some of the current investigations focus on cytokines and cell populations known to be abnormal in SS.

Interferon signature is a consistent finding in patients with SS, however the role of type 1 and type II interferons may vary in different stages of SS [381,395,534,535]. Some open labeled studies have proved that IFN-α given at low dosage by the oral-mucosal route can significantly increase UWS flow in patients with primary Sjögren's

syndrome, without causing significant adverse events [536]. At the same time, inhibitors of type I interferon, sifalimumab (anti-IFNα mAb), rontalizumab (humanized IgG1 anti-IFNα antibody) and anifrolumab (anti-interferon receptor 1 (IFNAR1)) are being studied [537–539].

Various cytokines besides the interferons have been shown to be elevated in patients with SS. These include TNF-a, lymphotoxin, IL-6, IL-7, IL-10, IL-17, IL-21 and IL-22 [540–544]. The TNF-α inhibitor, etanercept, failed to improve clinical features of patients with SS, but it was only given to patients with well-established disease [545]. A monoclonal antibody blocking the IL-6 receptor, tocilizumab, has been used in isolated patients with SS, but has not had any large clinical trials in SS completed [546]. Monoclonal antibodies exist to block each of the other cytokines, but clinical trials in patients with SS have not been completed with any of them.

In terms of B cells, their importance in SS has been emphasized in various studies [331,547,548]. Clinical trials have evaluated blocking all B cell subsets with rituximab (anti-CD20) or blocking the B cell survival factor BAFF with belimumab. The clinical trials utilizing rituximab in SS patients had varying results depending upon whether patients were studied with early disease or well-established disease. Late stage patients showed no response, but patients with early disease demonstrated histopathologic evidence of reduced glandular inflammation and re-differentiation of lymphoepithelial duct lesions to regular striated ducts as a putative morphologic correlate of increased parotid flow and normalization of the salivary sodium content [549,550]. There is no doubt that rituximab is effective in SS when used in the right patients and at the right stage of the disease. Previous trials with belimumab improved certain laboratory parameters in SS but failed to demonstrate any clinical improvement [551,552].

The abnormal development or differentiation of T cells in SS has been shown in basic studies [553–555]. Low-dose IL-2 was given to patients with SS to enhance Treg function. Treatment was well tolerated and improvement was seen in ESSDAI and ESSPRI scores, pulmonary and renal tubular abnormalities, arthritis, thrombocytopenia, leukopenia and fatigue. Immunological analyses revealed that low dose IL-2 treatment led to expansion of regulatory T (Treg) and B10 cells and the reduction of IL-17A and IFN-α (Jing He et. al. *Low-dose IL-2 treatment in patients with primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial*, in press 2019). Other T cell targeted trials have been conducted recently, although none of them lead to acceptable results, either because of toxicity or lack of efficacy: alefacept (monoclonal antibody that blocks the interaction between Leucocyte Function-associated Antigen, LFA-3 and CD2) [556], efalizumab (humanized monoclonal antibody targeting the CD11 component of LFA1) [557], otelixizumab and teplizumab (humanized monoclonal anti CD3 antibodies) [558,559].

Improved understanding of SS relies on ongoing research in all the areas highlighted in this review. Furthermore, advances in cell biology, molecular biology, microbiology and other fields of science are likely to contribute to advances in our understating of the complex pathophysiology of SS and the variability in its expression in different patients. Novel therapeutic approaches will evolve from this research.

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