Sjögren's Syndrome Textbook
by Stone, Casal, and Moutsopoulos

Chapter: **Therapy of Oral and Cutaneous Dryness Manifestations in Sjögren's Syndrome**

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Key Words

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Dirunal variation of saliva flow
Burning Mouth Syndrome
Xerosis
Vaginal dryness

ABSTRACT

Treatment of oral dryness in the Sjögren's syndrome patient remains unsatisfactory. A variety of methods including *mechanical stimulation of*

the oral mucosa with sugar-free lozenges, *mechanical devices, topical lubricants* to facilitate chewing-swallowing-speaking, and *oral agents to increase salivation* by augmenting cholinergic function are currently used.

New approaches in early clinical trial include:

1. agents that impede water loss across the mucosal membrane by sodium-linked channels; and
2. stimulation of water transport directly across the mucosal membranes by purogenic stimulated water transporters.

Rheumatologists must recognize that **a dry mouth is not necessarily a painful mouth** and that oral candidiasis is a frequent treatable cause of increased symptoms.

This *erythematous candida* infection often occurs under the dentures in the SS patient in a location that is not part of the normal rheumatologic exam. Additionally, when prescribing medications for the SS patient, potential anti-cholinergic side effects and normal diurnal variation of salivation must be considered.

In many SS patients, the symptoms of dryness are out of proportion to either clinical exam or results of salivary scintography. This may reflect the importance of mucosal mucins to reduce the viscosity of movement of tongue and membranes. Also, the painful mouth may result from “burning mouth” syndrome, which includes a spectrum of causes from localized neuropathy to depressive syndromes.

Although specific dental aspects are best addressed by the Oral Medicine Health team, the rheumatologist frequently will be asked by the patient about their additional particular oral needs due to both their dryness and their systemic medications. Particularly, recommendations regarding fluoride treatments, agents to improve calcification, the use of cosmetic dentistry and implants are important and expensive topics to the patient.

Also, simple instruction about their particular needs at the time of surgery (such as the ability to use oral lubricants while they are water intake restricted) and attention to methods of intubation in order to preserve teeth/dentures may be save expensive reconstructive surgery at a later date.

Other dryness complaints of the SS patient include dry skin (xerosis) and vaginal dryness. Although these are best evaluated by the dermatologist and gynecologist, the rheumatologist must be familiar with the treatments used by other specialists.

I. Background

Sjögren's syndrome (SS) is characterized by dry eyes and dry mouth. This chapter will concentrate on the treatment of dry mouth and the particular needs that the patient can perform for themselves and the special attention by the dentist and oral hygienist required as a consequence of dryness.

The importance of oral dryness extends far beyond simple difficulty in eating certain foods or increased frequency/expense of dental problems. Women socialize around eating, and thus, the inability to eat the same foods with family and friends impact on their overall quality of life, as measured by the "Oral Health Quality»\Assessment Scales."

Increasingly, women engage in "working" breakfast, lunch and dinner meetings, as well as the need to give oral presentations. All of these activities are profoundly impacted by dry mouth and difficulty with talking due to oral dryness. For example, it may be necessary to pause for a sip of water every few sentences in order to be able to spend hours on the phone or give public presentations. Tooth loss not leads to expensive and often painful dental restorations, but also may alter the nutritional intake, as patient is unable to chew or swallow particular foods.

A first step in effective management of SS is the recognition of medications with drying anti-cholinergic side effects (including over-the-counter sleeping aids), as well as consideration of diurnal variation in salivary flow rates with decrease in basal secretion at night and accompanying sleep disturbance.

Thus, medications with these side effects should not be given at a time when the effects will be additive with the decrease salivation at night. The interruption of sleep due to dryness may result from a vicious cycle of drinking more water and polyuria that leads to morning fatigue. Thus, patients might be encouraged to drink less water after dinner and use oral lubricants in order to avoid sleep disruption due to need for urination.

The treatment of dryness symptoms remains unsatisfactory, due in part to the poor correlation of patient symptoms of oral discomfort with objective measurement of salivary flow rates. There is a general misconception that dryness results from the destruction of the salivary glands, when only about 50%

of the acini/ductal cells are destroyed in patients with severe dryness. This points out the importance of the inflammatory process on the neural innervation and post neural salivary gland function induced by local production of cytokines and metalloproteinases.

However, symptoms of dry mouth (like dry eyes) are dependent on a “functional circuit” where afferent nerves from the mucosal surface travel to the midbrain (salvatory nucleus) which also receives input from higher cortical regions (including taste, smell, anxiety and even auditory-- as Pavlov illustrated in his famous experiments where ringing a bell led to salivation in dogs).

This discrepancy between symptoms and signs of dry mouth is extremely important clinically. It is most apparent in those patients with “burning mouth” syndrome, where severe symptoms are not accompanied by objective evidence of oral dryness on exam or a dramatic decrease in the flow salivary flow rate by scanning technique. This emphasizes the role of the central nervous system (central sensitization) or localized neuropathy in the generation of symptoms and how the patient perceives the severity of “dryness sensation.” Patients with clinical depression, neuropathy, Alzheimer's disease (even in the presence of drooling), and multiple sclerosis frequently have complaints of dryness.

Therapeutically, treatments for dry mouth include topical agents to lubricate and facilitate swallowing and talking. Oral agents may increase the cholinergic innervation of the glands. Since limited time during the patient’s rheumatology clinical encounter does not allow detailed patient instruction, we have used ***email*** as a highly effective means of providing instructions to the patient about where to purchase certain products and what precautions need to be taken to prevent tooth loss.

Over the past 20 years, a variety of mechanical devices placed in the mouth have been shown to stimulate basal saliva flow. This emphasizes the role of mechanical stimulation such as brushing the tongue and buccal mucosa, as well as frequent use of sugar-free lozenges.

In addition, other sicca symptoms include dryness of the skin (xerosis), nasal dryness, and vaginal dryness. The need to keep the nasal passages clear and moist will prevent mouth breathing, particularly at night, when the basal secretory rate is diminished. Also, the role of smell is closely linked to gustatory stimulation.

II. General Approach to Dry Mouth

A. Oral Hygiene and Self-Care by the Patient

Approaches to clinical management of oral sicca symptoms are generally the same for primary or secondary SS. The quality of information available from resources on the Internet or from patient support groups varies widely.

Current recommendations by the American Dental Association include:

- *Use of dental floss after EACH meal, AND fluoride-- either as toothpaste* or a mouth rinse daily.
    - *Carrying a portable toothbrush and fluoride toothpaste is a very worthwhile practice* in this case.

- *Avoidance of sucrose, carbonated beverages, juices, and water with "sweetener" additives.*

- *Avoidance of oral irritants* (e.g., coffee, alcohol, and nicotine)

- *Maintenance of good hydration* by taking regular sips of water and drinking sugar-free liquids (See "Fluids" below.)

- *Use of toothpastes specifically designed for dry mouth, which lack the detergents* (such as sodium lauryl sulfate, which is the foaming agent in most toothpastes)[28]. These substances, that are present in many types of toothpaste, can irritate the dry mouth. [29](6, #15969).

While infrequent, we caution patients that some of the fluoride-containing toothpastes *may* lead to brown discoloration of the teeth. Many of these "dry mouth" toothpastes are widely advertised, but have not been carefully studied in terms of their outcome for dental caries or tooth loss.

- One commercially available toothpaste (i.e., Biotene®), was found to give improved symptomatic relief in SS patients, although no change in the microbacterial composition of the biofilm was noted [29].

We also encourage our patients to use toothbrushes with features that improve effectiveness, such as inter-dental brushes (for cleaning between teeth) and electric toothbrushes.

[Please see suggestions listed in *Table 3 for Dental Products]*

A number of basic measures are used to prevent as well as treat dry mouth in those with SS. The published evidence supporting these measures is limited, largely consisting of clinical experience and small case series in SS [19]. Several older double-blind studies in SS patients demonstrated that the addition of mucins to carboxymethylcellulose (CMC) was superior to CMC alone [20-22]. A small single-blinded study using a commercially available product (Oral Balance®) also showed symptomatic benefit [23].

The following *measures for **prevention of dryness**, stimulation of secretions, dental prophylaxis, and attention to complications*, should be used in all patients with dry mouth due to SS, regardless of symptom severity:

- Avoidance of medications that may worsen oral dryness, especially those with anti-cholinergic side effects. These include over-the-counter antihistamines, cold and sleep remedies;
- Avoidance of smoking and alcohol;
- Maintenance of open nasal passages to avoid mouth breathing (see 'Nasal Dryness' below).
- Use of room cold humidifiers, particularly at night, in areas that are dry or windy;
- Stimulation of salivary secretions, using sugar-free salivary stimulants (e.g., chewing gums and lozenges);
- Careful chewing of food before swallowing (see 'Topical Stimulation of Salivary Flow' below);
- Meticulous oral hygiene and regular dental care, and avoidance of pre-processed "soft" foods that may be high in sugar content (see 'Basic Dental Care' below and 'Prevention of Dental Caries' below).
- Recognition of oral candidiasis that may mimic or exacerbate dry mouth symptoms (see 'Oral Candidiasis' below).

Various solutions --ranging from water to forms of artificial saliva-- can be used to *replace oral secretions*. We suggest frequent sips of water, because of convenience, low cost, and efficacy. The water does not have to be swallowed, but can be rinsed around the mouth and expectorated. Although water provides temporary moisture, it does not provide the lubricating properties that are characteristic of the mucin/water mixtures that constitute normal saliva.

Patients should be aware that too-frequent sipping of water may actually *reduce* the mucus film in the mouth and *increase* symptoms. If water consumption is excessive, especially in the evening, nocturia can occur, resulting in sleep

disturbance that may worsen fatigue, cognitive difficulties, and pain that some patients experience.

We advise patients to avoid acidic beverages, which may adversely affect dental enamel. Examples of common beverages and their relative acidity include:

- Cola drinks pH 2.6
- Coffee pH 5.0
- Tea, herbal pH 3.2
- Tea, black pH 5.7 to 7.0
- Water from tap pH 7.0 (but flavored waters are often acidic)
- "Energy drinks" usually acidic

The maintenance of pH in the oral cavity is highly important. When the pH in the oral cavity is stable, there is a decrease in the amount of demineralization that takes place. The pH and buffer capacity in the parotid saliva of individuals with Sjögren's syndrome are much lower when compared with those in normal control individuals. The buffer systems responsible for the human saliva-buffering capacity include bicarbonate, phosphate, and protein. Even a minor drop in pH can result in dental caries or damage to the teeth by erosion (Pedersen, 2005 #47).

III. Additional Needs of the SS patient from the Dentist

A. Background

At most medical centers, and for rheumatologists in practice, communication with dentists and specialists in Oral Medicine is quite limited. However, rheumatologists need to be familiar with the terminology used by Oral Medicine in order to read the relevant literature published on SS, and to advise patients regarding particular dental procedures that may influence their medical status. Radiation therapists have developed a close working relationship with Oral Medicine to prevent and treat oral complications, but a similar interaction for rheumatologists remain uncommon. Therefore, we will review basic terminology and approaches as a background to specific discussions listed below.

Tables 1-2 present a series of items that the rheumatologist may need to understand in order to effectively communicate with the dentist. These items -- not usually addressed in the training of internists or rheumatologists-- include:

- The contents of saliva
- Biofilm
- Dental plaque and accelerated caries

- Structure of dental enamel and its dissolution based on low pH
- Role of Fluoride
- Dental restorations including veneers
- Whitening or bleaching agents for cosmetic dentistry

Patients may require:

- additional visits for their oral hygiene, ranging from every 3 to 6 months;
- topical fluoride treatment after their dental cleaning;
- use of a stronger fluoride applied by dental trays used at night;
- use of calcifying agents such as MI paste;
- topical antibiotics to retard gum recession.

In individuals with Sjögren's syndrome, there is an increase in dental caries, (usually root and incisal caries [64]), appearing as destruction around the necks of the teeth and even on the labial and incisal surfaces (Newbrun, 1996 #48).

Dental plaque, consisting of more than 500 species of bacteria in a mature state, is a complex biofilm of microbes that adheres to the surfaces of teeth and provides a reservoir for oral microbial pathogens (Paster, 2001 #49). *Streptococci* account for approximately 20% of the total number of oral bacteria, and they are predominantly the first colonizers of freshly cleaned enamel surface. These bacteria are also the primary causative agents of biofilm formation and dental caries.

The bacteria normally are dislodged and expelled from the tooth surfaces and oral cavity by the mechanical forces of salivary flow and tongue movement (Daniels, 1992 #50). The alteration of bacterial flora occurs with dryness due to causes other than SS, including anxiety or medications (Bergdahl, 2000 #51).

Sjögren's syndrome, as well as other conditions including xerostomia associated with aging, also increases a person's likelihood of contracting opportunistic infections such as candida and the proliferation of cariogenic micro-organisms (Astor, 1999 #52). Persons with primary Sjögren's syndrome have been reported to have higher numbers of cariogenic and acidophilic micro-organisms in comparison with those found in control individuals (Pedersen, 2005 #47). A comprehensive study, carried out with interviews and clinical oral examinations of 53 persons with primary Sjögren's syndrome and 53 age-matched control individuals, found that those with primary Sjögren's syndrome had more teeth extracted, more problems with their teeth in their lifetime, and higher dental expenses, compared with the control group.

In a separate study (Christensen, 2001 #53), the number of decayed, missing, or filled teeth was higher in both the younger and older groups of persons with

primary Sjögren's syndrome, compared with the normal control individuals. The young persons had, on average, 7 teeth missing, compared with 2 missing in the control individuals. Those with primary Sjögren's syndrome had more frequent dental visits compared with control individuals.

Even with excellent oral hygiene, individuals with Sjögren's syndrome have elevated levels of dental caries, along with the loss of many teeth early in the disease. Pedersen *et al (Pedersen, 2005 #47)* reported that persons who brushed their teeth with toothpaste containing fluoride and visited their dentist more frequently, *still* had higher numbers of missing, filled, and decayed teeth, along with a higher gingival index.

Although specific recommendations should generally be made by the dentist, who is able to monitor the patient's response to dental treatment, medical clinicians should be aware of several *aspects of dental care of particular importance in SS* [2].

The loss of teeth in SS patients results from a combination of low oral pH that facilitates loss of dental calcium and alterations of oral bacterial flora that lead to accelerated decay. For individuals with very low salivary production, the amount of phosphate and calcium available for incorporation onto the tooth surface may be limited. The remineralization process may benefit from provision of calcium phosphate ions through toothpaste, specialized chewing gums, or as an oral solution. No long-term clinical trials have been done to test the effectiveness of these agents [5,25,26].

Fluoride is an important element in the prevention of dental caries [27]. However, certain regions do not maintain fluoridation in the water supply; patients living in these areas are at particular risk.

The increasing use of non-fluoridated bottled water in place of fluoridated tap water is having a profound effect in decreasing fluoride exposure for many patients.

Topical fluoride promotes remineralization of teeth by the development of a crystalline protective veneer at the site of demineralization and inhibition of bacterial metabolism and acid production. Fluoride may be applied in various forms, depending on the severity of disease, including mouth rinses, fluoride gels applied at home in custom-fitted trays, and by dental office-based application of fluoride varnish [2,28].

Chemoprophylaxis — Several approaches may be taken in an effort to reduce oral bacterial flora, including the use of *chlorhexidine (CHX)*, a topical antimicrobial agent, and products containing baking soda, bicarbonate or xylitol (see below) [2,29]. In addition, CHX has an antifungal effect that may also benefit

patients with SS. CHX may also be used to soak dentures overnight. Dentures may be a source of bacterial infection as well as recurrent *candida* infection, and patients should not wear dentures overnight.

Polyol sweeteners such as xylitol and sorbitol that are not fermentable by acid-producing bacteria, are of low cariogenic or noncariogenic potential; they may prevent or limit demineralization and promote the remineralization process [30-34]. Xylitol may be a useful adjunct to other anti-caries treatments, but should not be considered in patients with SS as a substitute for fluoride or other well-established interventions [2,30].

Patients with SS may have more difficulty wearing dentures because of the decreased moisture in the mouth. No adequately controlled clinical trials have addressed this question. In general, dentures cannot replicate the efficiency and comfort of natural teeth.

There are scattered case reports regarding the ability of patients with SS to handle implants, although the often poor status of oral tissues and bone loss in SS patients may cause difficulty. The majority of reports for SS patients appear favorable, but do not provide long-term follow-up [35]. Decisions regarding use of implants in a given patient with SS should be made on an individual basis, and the limited evidence should be acknowledged.

The safety of home products for whitening or brightening of teeth in patients with dry mouth and salivary gland dysfunction has not been studied. However, *the use of such products should be avoided,* since there may be increased risk from the acidity of some over-the-counter products designed for use in patients with normal salivary flow and content.

If *professionally applied whitening processes* are considered, the use of a remineralizing solution containing calcium phosphate and a fluoride treatment may be beneficial in conjunction with a bleaching treatment. Such procedures should only be performed after consultation by the patient with their dry mouth dentist.

IV. Particular oral needs of the SS patient to be assessed by the rheumatologist

The *particular needs for evaluation and treatment* in SS patients by the rheumatologist are summarized in ***Table 3***. These include:

- Recognition of oral candidiasis, particularly under dentures;

- Need for secretagogue therapy;
- Recognition of “burning mouth syndrome” out of proportion to objective dryness;
- Recognition of medications with anti-cholinergic medications (often from other physicians).

The response to therapy may be evaluated by *ongoing assessment for common* ***clinical signs of dry mouth***. These include:

- Difficulty with swallowing or speech due to dryness;
- Absence of a pool of saliva on the floor of the mouth;
- "Lipstick sign" (spreading of the patient's lipstick onto teeth);
- “Sticking” of a gloved finger to the mucosa;
- Frequent occurrence of *erythematous candida;*
- *Atrophic glossitis* (or lack of papilla) on the tongue;
- Dental caries at the gingival margin, especially of the mandibular incisors.

V. Use of Secretagogues

In patients who do not respond adequately to the basic measures described above, and those who continue to have signs or symptoms of dry mouth despite the measures noted above, we suggest additional measures, including the use of *muscarinic agonists as sialogogue*s

Use of a systemic sialogue (administered orally) is indicated in patients with more than very mild salivary dysfunction, who do not achieve sufficient salivary excretion with topical stimulants such as those described above. Two muscarinic agonists, pilocarpine and cevimeline, increase salivary flow and improve symptoms of dry mouth (8, #15969). ***Pilocarpine*** and ***cevimeline*** are most effective in patients with greater residual excretory capacity (1, #15969).

These agents are most useful early in the course of SS, while the patient still has baseline and stimulated saliva [33-39]. A double-blind trial has recently been reported for a *buccal insert that releases pilocarpine* [40].

Their use may sometimes be limited by poor tolerance, largely due to cholinergic side effects including undesirable increased/excessive perspiration. Although very uncommon, patients should also be cautioned about driving at night or performing hazardous activities in reduced lighting, because they may experience *altered visual acuity or impaired depth perception*.

Due to the potential for pilocarpine to stimulate the muscarinic M2 receptor, theoretical cardiac or lung (asthmatic) complications) might occur, and therefore, patients with these historical features were excluded from clinical trials of pilocarpine or cevimeline [37]. However, clinical practice with these agents in patients with radiation xerostomia (who frequently have a long history of smoking and cardiac disease) has not shown this to be a clinically significant problem [37].

Cevimeline is taken three times a day (optimally about half an hour before meals), and can be taken up to four times a day (including an additional tablet at bedtime to help with nocturnal dryness). Cevimeline has a longer half-life in serum, and longer occupancy on receptor, which correlates with patient salivation profile [34, 35, 37]. Pilocarpine is taken four times a day, and the patients typically experience a brief "spurt" of saliva due to its relatively short half-life in the sera [35, 37].
The two drugs have not been compared directly. Issues that determine choice principally include cost to the patient, convenience, individual clinical response, and tolerance of adverse effects.

The choice of drug is often dictated by the patient's medical insurance plan medication Formulary. If pilocarpine is on Formulary (even though it is often more expensive, since taken four times a day), I try the pilocarpine first in order to help get prior approval of cevimeline.

The choice between pilocarpine and cevimeline is largely determined by individual factors, since both appear similarly effective, although it has been the experience of several SS centers that *the longer half-life of cevimeline leads to improved tolerance and lower side effects.*

Some patients do not respond sufficiently well to the muscarinic agonists to justify continued use, especially when cholinergic side effects are present. *However, in those with an inadequate response, it is important to examine the patient carefully to rule out* ***oral candidiasis****, which may be responsible for a lack of symptomatic improvement with use of a secretagogue*. The examination should include removal of upper dentures and determining if signs such as *angular cheilitis* are present.

When starting therapy with these agents, we *increase the dose gradually* (starting once/day for a week, and using a proton pump inhibitor if needed) to avoid gastric bloating and sudden onset of sweating. We suggest a trial of at least three months duration if the medication is tolerated, since the response is frequently delayed. **NOTE: Au, if a patient does not respond or tolerate one agent, do you switch to the other?** If the patient does not respond to pilocarpine (or has side effects), the patients may still exhibit benefit from

cevimeline, based on the number of patients in the double-blind cevimeline trial who has previously "failed" pilocarpine [31].

Pilocarpine, a muscarinic agonist that stimulates predominantly muscarinic M3 receptors, can significantly increase aqueous secretions in patients with residual salivary gland function [9-12]. The usual dose is 5 mg three or four times/day. It is most effective when taken four times/day because of its short duration of action. We thus suggest that patients try to take the medication four times daily if they do not receive adequate symptomatic relief with three times daily dosing. Side effects, including sweating, abdominal pain, flushing, or increased urination, may limit its use. In some patients with unacceptable levels of side effects at the full dose, a reduced dose of 2.5 to 3.75 mg three times daily, or 5 mg twice daily may still provide benefit [2,13].

In addition to effects upon xerostomia, pilocarpine may improve symptoms of ocular dryness, although without any objective change in tear production [13].

In the largest randomized trial that demonstrated the benefit of pilocarpine, 357 patients were randomly assigned to receive either pilocarpine (5 or 2.5 mg every 6 hours) or placebo for 12 weeks (9, #15969). The following findings were observed:

- *A significantly greater proportion of patients receiving pilocarpine (5 mg), compared with those who received placebo, experienced improvement* in global assessments of symptoms of both dry mouth and dry eye (61 versus 31, and 42 versus 26 percent, respectively).
- There was no difference in benefit found between pilocarpine 2.5 mg every 6 hours and placebo.
- Sweating and increased urinary frequency were both more common with pilocarpine 5 mg compared with placebo (43 versus 7 and 10 versus 2 percent, respectively).
- No serious adverse events occurred, and only 3 percent of patients taking pilocarpine 5 mg withdrew from the study due to drug-related adverse events.
- The overall withdrawal rate did not differ between the three groups (6 to 7 percent).

There are no published studies that have examined the long-term efficacy of pilocarpine in patients with Sjögren's syndrome.

Cevimeline, an effective sialogogue, is a derivative of acetylcholine with a higher affinity for muscarinic M1 and M3 receptors on the lacrimal and salivary epithelium than for receptors on cardiac tissue [14]. Doses of 30 or 60 mg three times daily *alleviate the symptoms of dry mouth, dry eyes, and stimulate salivary*

flow. The 30 mg dose is nearly as effective as the higher dose and is better tolerated [15]. We suggest dosing at 30 mg three times/day.

When initiating therapy, we suggest gradually increasing the dose and taking it about *30 minutes before meals*.

Initially, some patients experience dyspepsia, which can be minimized by use of a proton pump inhibitor (such as *omeprazole)*, while initiating therapy and taking it with food, (however, some patients may respond better to longer-acting non-generic proton pump inhibitors).

Major side effects of cevimeline include excessive sweating, nausea, rhinitis, diarrhea, and visual disturbances. Use of lower doses in patients with poor tolerance of the full dose have been reported. Efficacy in lower dosing is obtained by dissolving the desired fraction of a 30 mg capsule's contents in water, or to employ a "rinse-and-spit" regimen to minimize systemic absorption [2].

In randomized placebo-controlled trials, cevimeline significantly increases salivary flow and patient “oral quality of life" [15-20]. The efficacy of cevimeline was illustrated in a study that randomly assigned 197 patients with either primary or secondary SS, to cevimeline or placebo [16]. The following outcomes were observed:

- Patients' global assessments of dryness were improved significantly more often by cevimeline 30 mg three times daily than by TID doses of 15 mg or placebo (65, 32, and 35 percent, respectively).

- The most common adverse events seen more often with the drug (30 or 15 mg TID) than placebo, were nausea (21 and 12 versus 7 percent), increased sweating (18 and 5 versus 1 percent) and diarrhea (16 and 14 versus 7 percent).

- Withdrawal from the study for adverse events was more common in patients on cevimeline (30 or 15 mg TID) compared with placebo (16.1 and 13.8 versus 4.3 percent, respectively).

- Serious adverse events were seen in <3 percent of patients, and were not more common with cevimeline.

Drugs that inhibit cytochrome CYP2D6 and CYP3A3 also inhibit the metabolism of cevimeline. Individuals who are known to be deficient in these cytochrome isoenzymes should use cevimeline with caution.

OTHER CHOLINERGIC AGONISTS

Bethanechol and ***pyridostigmine*** are cholinergic agonist agents that are approved in the U.S. for use in urinary retention and myasthenia gravis, respectively, but *not* for SS. They have mixed muscarinic and nicotinic activity, and are used much less often for SS because of *greater adverse effects* compared with pilocarpine and cevimeline (1, #15969). However, they have been shown to provide palliative care of radiation xerostomia in small double-blind studies [41, 42].

Amofostine is an agent that may provide protection of the salivary glands during radiation therapy[43], but was not as effective as pilocarpine in patients with xerostomia after radiation[44].

Bromhexine (a mucolytic agent) has also shown palliative response in radiation xerostomia, and had been suggested for symptomatic treatment in SS [45]. However, this agent has now been withdrawn from the market. **(NOTE: Au, do you ever use these agents? If so, in which patients? Thanks)** Although these agents have theoretical benefit, they have not been subject to controlled clinical trials in SS. Anecdotal trials of these agents in SS, as well as amofostine, have been disappointing in our clinic.

ADDITIONAL TOPICAL TREATMENTS

- Topical interferon alpha —

  Although *oral interferon* alpha was promising in early studies [22,23], results were far less encouraging in a subsequent larger well-designed study [24]. Further studies will be needed before this medication can be recommended in this setting. However, the use of interferon alfa in patients with hepatitis C and sicca symptoms has exacerbated their dryness complaints [46-50].;

- Accupuncture, anhydrous crystalline maltose, and masticatory and gustatory stimulation based on anecdotal reports (Wallace, 2005 #56) and electrical stimulation in a small double blind-study(Steller, 1988 #58);

- anetholetrithione- which exhibited modest benefit in a small double blind trial (Hamada, 1999 #59).

SYSTEMIC THERAPY

TNF-alpha blockers

Short-term studies with ***infliximab,*** a TNF-blocker, showed significant improvements in Sjögren's syndrome symptoms [51]. However, randomized, double-blind, placebo-controlled studies showed no indication of increased efficiency in persons treated with infliximab [52].

Randomized, double-blind, placebo-controlled studies with ***etanercept*** also showed no reduction of sicca symptoms in Sjögren's syndrome [53, 54].

Rituximab, known for its tolerance and short-term efficacy, is an anti-CD20 antibody that is effective in persons with various autoimmune diseases. Several controlled studies have shown a small increase in saliva flow in a subset of patients with early disease [55-57]. Also, salivary biopsies from treated patients have shown decrease in lymphocytic infiltrates[58-60].

Epratuzumab is a different antibody to the B-cell marker CD22, and appears to function, in contrast to CD20 antibodies, by modulation of B-cells than by their high depletion in circulation [61].

Steinfeld et al presented preliminary results in the treatment of primary Sjögren's syndrome including increased salivary flow in the drug treated cohort. The study consisted of 16 Caucasian individuals, two of whom discontinued due to complications. However, ten persons reported adverse events, which included acute infusion, dental abscess, transient ischemic attack with secondary seizure, and osteoporotic fracture. Non-serious adverse events included headache, paresthesia, and acute infusion reaction, which resolved quickly [62].

Recently, a monoclonal anti-BAFF antibody *(Benlysta)* has shown promising results in SLE [63] and studies are just starting with SS patients in France.

VI. Oral Candidiasis

Oral candidiasis is a common complication of SS, which may occur in over a third of patients [36,37]. Symptoms include a painful mouth, sometimes with a burning sensation, and sensitivity to spicy or acidic foods. Oral candidiasis is particularly frequent following antibiotic treatment or the use of glucocorticoids (see "Clinical Manifestations of Oropharyngeal and Esophageal Candidiasis").

Oral candidiasis is one of the most common oral infections. In 1980, an inverse relationship between salivary flow rates and the level of *Candida* infection was described (Tapper-Jones, 1980 #54). Also, persons with Sjögren's syndrome have been reported to have *Candida albicans* more frequently than the general population at a given salivary flow rate, indicating a role for qualitative anti-candida factors such as lysozyme content in SS saliva (Samaranayake, 1982 #55).

Findings in SS patients with oral candidiasis include diffuse or patchy erythema and, less often, white patches on the mucosal surfaces. The tongue, buccal mucosa, palate, lips and the corners of the lips may be affected. There may be loss of tongue papillae. Angular cheilitis and atrophic changes of the buccal mucosa are common manifestations in SS [37].

In patients with SS and oral candidiasis, several particular factors require consideration. Because most antifungal preparations for oral use contain sugar to improve taste, such agents should not be used immediately before bed without following with a thorough tooth brushing.

An alternative oral “off label” approach preferred by some experts is use of **topical Nystatin Vaginal tablets** (100,000 units/tablet) sucked on like a lozenge three to four times/day for seven to ten days [2]. These tablets do not contain fermentable carbohydrate in the carrier.

- We initially treat with *clotrimazol* (200 mg/day) for five days, and treat angular cheilitis using *topical clotrimazol cream*.

- *We advise use of an oral mouth rinse of the type recommended by radiation therapists for mucositis*. The rinse should be used for two minutes (rinse plus gargle) three times/day for two to three weeks. These rinses are known by various names, such as "Stanford Mouth Rinse" or "Miracle Mouthwash.” We use a mixture containing Mylanta (aluminum hydroxide/magnesium hydroxide) 240 ml (as a vehicle), diphenhydramine 20 ml, nystatin 20 ml, and doxycycline 20 ml. The components can be ordered separately and mixed by the patient. Variations of this mouth rinse may contain viscous lidocaine, low-dose glucocorticoids, or

brompheniramine/pseudoephedrine elixir (see "Complications of radiotherapy for head and neck cancer" section on 'Mucositis').

Several mouth rinses used by radiation therapists may also be helpful, as may a homemade remedy of 12 tsp. salt and 1/2 tsp. baking soda in 8 oz water, a wound rinse with aloe vera extract, and carafate suspension as a rinse used twice per day.

There is some concern in patients with severe salivary dysfunction that insufficient local (salivary) levels of medication may be reached with use of systemic medications. Thus, in dry mouth patients who do not respond adequately to systemic medications within seven to ten days, switching to a topical oral antifungal is suggested [2]. (See "Treatment of oropharyngeal and esophageal candidiasis", section on 'HIV-seronegative patients.')

- In patients with more persistent oral fungal disease, we recommend the use of **nystatin vaginal troches** (100,000 units) that are sucked on daily with water sweetened with an artificial sweetener (to improve the taste). Treatment twice daily for up to four to six weeks may be required.

- Alternatives include **miconazole oral gel** (sugar-free, 24 mg/ml = 20 mg/g), 5 to 10 ml four times/day, held in the mouth before swallowing; and **amphotericin lozenges** (10 mg) four times daily.

VII. Treatment and Management of CUTANEOUS Manifestations

A. Treatment of dry skin in Sjögren's syndrome is similar to managing xerosis in other conditions.

1. The patient should moisturize with a fragrance-free cream moisturizer once or twice a day. Moisturizing is performed immediately after bathing or showering, while the skin is still damp, to prevent further evaporation from the skin.

   Sometimes in cases of extreme dryness, an ointment is suggested, for its barrier and protective properties (such as petrolatum jelly or Aquaphor®).

   If ointment is used, then application should be onto damp skin, as the ointment itself does not contain water. Excess greasiness can be blotted with a towel.

Sometimes a moisturizing cream with beta or *alpha hydroxy acid*, or urea, can add extra moisture, but in cases of cracks in the skin, these will sting and irritate.

2. Excessive, long, hot showers or baths should be avoided, in addition to heavily fragranced cleansers.

3. Cleansing of the skin: The usual recommendation is to cleanse with a moisturizing soap such as Dove® fragrance-free bar, or a soap-free cleanser such as Cetaphil® gentle cleanser or Aquanil® cleanser.

If the xerosis leads to pruritis, then safe anti-pruritic topical treatments are recommended.

4. Over-the-counter lotions containing menthol, camphor (Sarna Anti-Itch Lotion®), 2% lidocaine (Neutrogena Norwegian Formula Soothing Relief Anti-Itch Moisturizer®), and pramoxine (Aveeno Anti-Itch Concentrated Lotion®) are readily available.

5. Oral antihistamines should be used with caution because of their anticholinergic effects. Fexofenidine (Allegra) does not cross the blood brain barrier and may have slightly less dryness as a side effect. Over-the-counter sleeping medications that contain hydroxyzine (Atarax) or diphenhydramine (Benadryl) are very drying, and may contribute to sleep disturbance.

6. Topical corticosteroids: We generally do not like to use topical corticosteroids, especially the ultra-potent ones, but even the mid-potency ones-- for more than a couple of weeks at a time. In the case of inflammatory skin findings, local treatment with potent topical steroids can augment systemic treatments.

Sometimes topical corticosteroids are used for pruritis, but their use should be limited due to long-term side effects such as skin atrophy, tachyphylaxis, and absorption.

7. We always suggest constant daily sun protection for patients with autoimmune conditions. Because the wavelength of light causing sun sensitivity in autoimmune conditions may not be in the UVB spectrum (290-320 nm), patients should use a broad-spectrum sunscreen.
    - SPF factors refer to UVB protection only, so patients cannot count on simply the SPF factor.
    - Most sunscreens available now have added UVA protection (290-320 nm), commonly from chemical UVA absorbing compounds, such as Parsol 1789 (avobenzone).

8. We prefer physical sun blocks, since wavelengths outside of both UVB and UVA may affect the patient with autoimmune disease.

    - Physical sun blocks contain titanium dioxide or zinc oxide, which reflect rays.
    - One commonly available sun block is Neutrogena Sensitive Skin Sun Block SPF-30®, which uses purely titanium dioxide as its active ingredient.

9. The most effective protection is sun-protective clothing, since it will not wear off as sunscreens do.

    Obviously, avoiding excess sun contact altogether is prudent, such as trying to stay indoors during the intense sunlight hours of 10 AM to 2-4 PM.

10. Mucous promoting compounds. Study of the tear film and saliva have shown that SS symptoms are more than the simple absence of acqueous secretions. In particular, the lubricating film contains a series of mucins and proteins in an emulsified gel. A lipid layer prevents subsequent evaporation. As many of the extraglandular symptoms of SS may result from decreased lubrication, such chronic upper airway dryness or vaginal dryness, these agents may part of future treatments.

Agents that are currently in trial (particularly for oral and ocular) include:

a) **diquafosol**, an agonist of the P2Y2 receptor that stimulates net chloride transfer from the serosal to the mucosal side of epithelial membranes.

b) **15-S Hete**, an arachadonic acid metabolite, acts as a mucin secretagogue and has been shown to stimulate mucin I production.

c) **rebamide, ecabet sodium** and **gefarnate** have been used in Japan as gastroprotective agents because of their mucus secretary action.

B. RAYNAUD'S

Raynaud's has been reported in 30% of patients with primary SS. The clinical course of Raynaud's phenomena in most SS patients is often milder than in patients with scleroderma. It is often an early sign and may be apparent before symptoms of clinical sicca are apparent. However, some patients do develop severe Raynaud's and digital ulcers even though they lack other clinical features suggestive of scleroderma.

The use of protection including gloves, especially when spending excess time in the freezer section of the supermarket, and moisturizers to prevent skin cracking must be emphasized. The use of moisturizers to the fingertips is increasingly important, as SS patients spend increasing amounts of time using either their computer keyboard or "text messaging" on their cell phones (explaining in part the sudden increase in trauma pain in the thumbs used for "keying text" to other friends).

Treatment of Raynaud's in SS

Of SS patients with Raynaud's, about half will require pharmacologic treatment, initially using calcium channel blockers. Avoidance of caffeine, smoking and herbal medications also may play a role in improvement of symptoms. For more severe cases, treatment similar to that used in SLE or PSS, including ganglionic blocks, iloprost, and use of endothelin antagonists and sidenifil may be required {Launay, 2007 #16270;Hachulla, 2004 #13281;Badesch, 2004 #13283;Leighton, 2001 #10205}.

C. Vaginal Dryness

A gynecologic exam is useful to rule out other causes of painful intercourse and other causes of vaginal dryness.

When it does occur as part of Sjögren's syndrome, the spouse or partner needs to be reassured that this is a "physiological" problem and not related to a failure of sexual arousal. Sterile lubricants such as

Astroglide®, KY Brand® jelly or Surgilube® are helpful (should be liberally applied to both partners for maximal comfort) {Carsons, 2001 #17122;Graziottin, 2001 #17126}.

The Sjögren's patient currently has many more options regarding safe and effective vaginal lubrication than ever before.

Lubricants such as Maxilube® and Astroglide® have slightly different characteristics when compared with KY Brand® jelly or Surgilube®, and yet share the common characteristics of being water-soluble and non-irritating. This also holds true for the new non-hormonal vaginal moisturizer Replens®, which may be used, unassociated with intercourse. For those patients who do not like the gel-type lubricants, there is now available Lubrin® vaginal inserts.

Finding the right preparation for a specific individual is often a matter of trial and error inasmuch as satisfaction with each lubricant is a matter of personal preference. The patient needs to be frank with her physician regarding her satisfaction or dissatisfaction with a particular preparation.

The external use of preparations containing petrolatum or oils that "seal in" moisture, such as Vaseline® or cocoa butter, as well as "scented" or "flavored" preparations, may lead to maceration and irritation of the vaginal lining, and are to be avoided.

Vaginal dryness in perimenopausal or postmenopausal women is often related to vaginal atrophy because of declining estrogen levels, and therefore responds to vaginal estrogen creams such as Estrace®. Cortisone creams are not beneficial in this situation.

If vaginal yeast infection occurs, prompt treatment with clotrimazole topical cream, vaginal suppositories (Gynelotrimin®), or p.o. gluconazole 150 mg is safe and effective. Oral gluconazole's benefit is that it can be started earlier in the day, rather than waiting until bedtime to use cream or suppository. With yeast infection, prompt treatment is essential to avoid rapid escalation of the infection during the day, along with higher level of discomfort for the patient.

On the external vulvar surface, dryness may be treated with lubricating creams, as would other skin surfaces (see section on skin dryness). Several patients have reported considerable satisfaction with the use of a thin film of vitamin E oil {Fleming Cole, 2001 #17125} used on the vulva once or twice a day.

An issue of concern to female Sjögren's patients has been whether or not estrogen replacement therapy at the time of menopause is harmful to their condition {Johnson, 2000 #8454}. With regards to estrogen replacement in general, the clinical evidence is controversial whether the risks of blocking osteoporosis and reducing cardiovascular mortality adequately offset the small increase in risk in breast cancer.

It is also worth noting that the subset of women who had previous hysterectomy/ovariectomy were not found to have increased risk of breast cancer on receiving estrogen replacement {Colditz, 1995 #17123}.

Of importance, some women feel that estrogen replacement improves their quality of life, in terms of mood elevation and by reducing hot flashes and hormone-related vaginal dryness {Buyon, 1995 #17120;Buyon, 2005 #17121;Petri, 2001 #12815}. Part of this improvement may relate to the interconversion of hormones to include DHEA, which appears to have beneficial effects on local mucosal surfaces {Sullivan, 2003 #17141} as well as affect {Petri, 2002 #17139}.

Earlier investigators were concerned that estrogen might have a negative influence on Sjögren's or SLE based on animal studies. At our clinic, we have not seen any deterioration of Sjögren's syndrome related to either estrogen replacement therapy or low estrogen forms of oral contraceptives.

Because of this, we encourage adequate estrogen replacement for the properly screened postmenopausal Sjögren's patient who feels that it improves their quality of life. Although the data has not been formally collected in SS, there have been extensive trials on the use of oral contraceptives and estrogen replacement in SLE patients {Buyon, 1995 #17120;Buyon, 2005 #17121;Petri, 2001 #11669}. These studies have indicated safety in terms of breast cancer and disease activity. However, caution with regard to blood clot risk remains, particularly in the patient with circulating anti-coagulants or a past history of thromboembolic disease.

Nonetheless, estrogens would not be the agent of choice to deal with either post-menopausal osteoporosis or elevated lipid profiles. Other therapeutic alternatives for osteoporosis (alendronate, Fosamax®, and residronate, Actonel®) and other agents for lowering cholesterol (such as statins) are now available, and estrogens are now not the agents of choice for these medical issues.

D. Special Precautions at the Time of Surgery

SS patients have particularly unique needs at the time of surgery. Patients with ocular dryness are at increased risk for corneal abrasions in operating rooms (generally have low-humidity environments), and particularly in the post-operative recovery room, where non-humidified oxygen is blown across their face at a time when they are still too groggy to have adequate blink reflex.

Therefore, we have recommended application of an ocular ointment or gel prior to surgery.

Patients are subject to severe dryness of the mouth as a consequence of their disease but are told to be "NPO" for at least 12 hours before surgery (and often longer if they are a later operative case in the day). We have found that patients can safely use their oral mouth sprays for comfort pre-operatively, while not having the risk of gastric contents and aspiration during anesthesia. If possible, patients should request from their surgeons that they be placed in an early slot in the OR schedule.

The anesthesiologist will need to take special precautions with oral intubations, as these patients have "fragile" teeth and often have expensive dental reconstructions including implants.

Therefore, it is important for the patient to make certain that a "heads-up" note is recorded in –or better yet-- on the front-- of the chart.

Patients with SS often have very dry upper airways and minimal use of anti-cholinergic agents to control tracheal secretions. The tenacious mucus secretions may predispose to mucus inspissations and post-operative obstructions. The use of humidified oxygen and mucolytics may help minimize this process.

Although anesthesiologists and surgeons are familiar with precautions regarding NSAIDs and bleeding risk, they are often less familiar with the relatively long duration of agents such as the new biologic agents. Although most of the literature about increased rate of infection after joint replacements deal with TNF inhibitors, it is likely that similar caveats will apply to additional biologic agents as they become available.

Finally, steroid coverage for "stress" levels may be required in patients on chronic steroids. Also, oral candida is quite common in the post-operative patient who has been on steroids and recent antibiotic therapy.

Patients should also be permitted to have their eye and mouth moisturizers and other appropriate remedies at bedside if hospitalized.

IIX. Vaccinations in the SS patient

Bob: need to complete this section!

IX. Summary

SS presents an immense time investment to manage its unique extra-glandular manifestations, and these manifestations will be unique to each patient.

With rheumatologists increasingly taking the lead in being both the diagnostician and clinician managing the broad spectrum of extraglandular manifestations of SS, it is paramount that rheumatologists broaden their knowledge base of SS and its wide spectrum of extraglandular manifestations, diagnostic procedures, and therapeutic approaches.

Among the many manifestations rheumatologists can expect to see and treat include: sicca symptoms (including eyes, mouth, vagina), arthralgias, myalgias, dysphagia, elevation of erythrocyte sedimentation rate (ESR) and polyclonal hyperglobulinemia, vasculitic skin lesions, pneumonitis, neuropathy, nephritis, lymphoma, interstitial pneumonitis, multi-focal leukoencephalopathy, Raynaud's, and Fibromyalgia.