PEARLS OF WISDOM (edited by John Stone)

Chapter:

Pearls of Wisdom and Myths

Regarding Sjögren's Syndrome

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ABSTRACT **(electronic version only)**

Sjögren's ("SHOW-grins") Syndrome (SS) is manifested by:

- ***keratoconjunctivitis sicca***
- ***xerostomia***
- ***characteristic auto antibodies*** including anti-nuclear antibody (ANA) and anti-Sjogren's syndrome A (SS-A) antibody.

Pathologically, biopsies of the lacrimal and salivary glands exhibit:

- focal infiltrations of *lymphocytes,
- changes in the vascular endothelial cells,
- alteration in glandular (acinar and ductal) elements, and
- disorganization of the extra cellular matrix of the glands.

The frequency of primary SS has been a source of debate during the past decade, based on the lack of a uniform set of criteria. According to the current American-European consensus criteria, it affects approximately 0.5% of women with peaks in the age groups of 25-35 yrs and in the 50-60 yr group. Although it also may occur in males, the female:male sex predominance is 9:1.

Myths and Pearls regarding SS generally fall into several groups:

- Diagnosis of disease and the relationship of SS to SLE, demyelinating disorders or fibromyalgia
- Laboratory Manifestations that reflect the difference between sensitivity and specificity of both anti-nuclear antibodies (ANA) and minor salivary gland biopsies
- Clinical Manifestations, particularly chronic fatigue and other neuropathic features, that occur in a patient with a positive ANA
- Pathologic-Clinical correlations that consider SS to be a simple deficiency of aqueous secretions of eye and mouth. In fact, the lubricating and protective capacity of tears and saliva depends on (a) mucin, (b) proteins, and (c) lipids. Further, SS patients have a higher incidence of lymphocytic infiltrative disorders, including lymphoma.

*KEYWORDS:

- **ACR:** American College of Rheumatology
- **Auto antibodies:** including anti-nuclear antibody (ANA) and anti-Sjogren's syndrome A (SS-A) antibody
- **Focal infiltration:** dense substances, such as pus, blood, water, or tissue that fills alveolar spaces
- **Lactimal gland:** small almond-shaped structure located just above the distal corner of the eye that produces tears

- **Lymphocytes:** white blood cells that play a large role in defending the body against disease the body against disease
- **Keratoconjunctivitis sicca***:* dry eyes
- **Mucin**: the inner most layer of tear film that serves as a lubricating aid. It is secreted by goblet cells that are on the surface of the eye. The mucin provides a protective barrier for the surface and serves as a means for the aqueous layer to adhere to the surface of the eye.
    - Mucins produced by salivary glands play an important role in oral health by coating the tooth surface and by acting as a bacterial receptor.
- **RA: Rheumatoid Arthritis:** a chronic, systemic autoimmune disorder that causes the immune system to attack the joints, causing inflammation (arthritis), and some organs, such as the lungs and skin. It can be a disabling and painful condition, which can lead to substantial loss of functioning mobility due to pain and joint destruction.
- **Sicca symptoms:** dry mouth and eyes
- **SLE:** Systemic Lupus Erythematosus
- **SS:** Sjögren's Syndrome

- **Vascular endothelial cells:** important signaling proteins involved in both formation of the embryonic important signaling proteins involved in both vasculogenesis (the *de novo* formation of the embryonic circulatory system and angiogensis (the growth of blood vessels from pre-existing vasculature).
- **Xerostomia:** dry mouth

I. Background (noting that Abstract is only in the electronic version)

One of the most prevalent myths about SS is that dryness results from the total destruction of the glands by the immune system (discussed further below). In fact, only about 50% of the glandular elements are "destroyed" in patients with severe dryness. and the remaining ducts/acini do not function because of the inflammatory process that disrupts the ability of the residual secretory units to either release or respond to neurotransmitters such as acetylcholine (Ach) and vaso-active intestive peptide (VIP).

SS can exist as ***a primary condition*** (1*SS) or ***as a secondary condition*** (2*SS) with *sicca symptoms* (dry mouth and eyes)/signs in association with other well defined autoimmune disorders such as rheumatoid arthritis (RA),

systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS), polymyositis (PM) or primary biliary cirrhosis (PBC).

Clinical Diagnosis

A. ***PEARL:***

In SS patients with florid dry eyes and dry mouth, parotid swelling and characteristic auto-antibodies, there is little debate over diagnosis.

The issue will be the extent of extraglandular involvement and the therapeutic options. In other patients, the rheumatologist may evaluate a patient referred with vague complaints of fibromyallgia and dryness, in association with the finding of a low titer ANA. In these patients, the diagnosis of SS (i.e.,, a systemic autoimmune process) is far from clear and the therapeutic decisions are more difficult.

B. ***PEARL:***

SS patients may see a myriad of health care specialists (rheumatologists, hematologists, pulmonologists, cardiologists, neurologists, otolaryngologista, gastroenterologists, dentists and other oral medicine specialists, in addition to their primary care physicians (PCP's).

Thus, the patient's clinical care is often fragmented, and patients frequently are given conflicting information. This misinformation is often compounded by the patient's frantic searches on the Internet, leading to retrieval of misinformation regarding diagnosis and treatment.

Instruct the patient to restrict their internet medical information searches to a much more reliable (albeit less well known) search engine "Google Scholar." http://www.googlescholar.com rather than using a more general search engine that frequently lead patients to Sjögren's syndrome "chat groups."

C. *PEARL:*

The most time consuming and often aggravating clinical problem is the assessment of the patient with vague myalgias and chronic fatigue (i.e., Fibromyalgia).

The rheumatologist must remember that these chronic complaints are often the most significant causes of "disability" from the patient's perspective. The differential can range from depressive to demyelinating disorders, as well as toxicities from other medications or herbal supplements. The rheumatologist will need to consider central nervous system vasculitis or

may suspect accelerated microvascular (atherosclerotic or micro-thrombotic) disease.

D. ***PEARL:***

Inform the patient with these concerns at the first visit that "fibromyalgia" represents areas of significant diagnostic and therapeutic controversy among rheumatologists.

Further, approaches to therapy must often be put off to the second revisit when further objective data is available to evaluate the correct diagnosis and disease activity. The patient can be directed to the Internet to read available patient information on validated sites such as:

- http://wwwWebMD.com
- http://www.MedScape.com
- http://www.eMedicine.com

II. Diagnosis criteria and Laboratory Tests

A. ***MYTH***:

MythBuster: *There is now a validated diagnostic criteria structure for Sjögren's syndrome that has been adopted by the *ACR.*

FACT: Although rheumatologists are using the European-US consensus criteria described by Vitali *et al.*[1], the *ACR has not yet accepted this criteria. Although the criteria have been validated in a European cohort, it has not been systematically studied in any US cohort. The European criteria are listed in Table 1.

B. *PEARL:*

There are recent criteria for disease activity and disease damage indices.

The same EEC consortium (Vitali *et al* [2]) that spearheaded the new consensus criteria have recently presented an activity and Disease Damage Index (Tables 2 and 3)[2] that will serve as a starting point for a uniform data base basis for clinical data collection and research studies. These indices will provide the same type of standardization that the *ACR criteria provided for *RA.

C. *PEARL:*

The diagnosis, activity, and damage score is more complicated to assess than simple *RA criteria.

This is predominantly due to the poor correlation of symptoms of dryness with objective findings and the large role that fibromyalgia plays in both the physician's and patient's assessment of "quality of life."

The problems in generating measures for evaluating *SS are more comparable to non--renal *SLE. Indeed, the new criteria for SS later are based on similar measures in SLE agents such as SELENA and Bilag, where the absence of definitive biomarkers has made disease assessment difficult. It should also be noted that the new measures extend the work of Bowman *et al*[3] in the development of a clinical disease activity index[3], that was acknowledged as a basis for the Vitali scores quoted above.

D. <u>MYTH</u>:

"The antinuclear antibody (ANA) and anti-Sjögren's SS-A (Ro) antibody are specific for primary Sjögren's syndrome."

<u>MythBuster</u>: Patients commonly arrive in the rheumatologist's office after the primary care physician has ordered a battery of tests for vague symptoms and a positive ANA and/or a positive anti-SS A (Ro) emerged.

ANA assays can be a useful in recognizing certain disease conditions, but can create misunderstanding when the limitations are not fully appreciated. The ANA has a higher sensitivity than specificity. Tan *et al*[4] measured the range of antinuclear antibodies (ANA) in "healthy" individuals.

- Fifteen international laboratories experienced in performing tests for ANA by indirect immuno-fluorescence participated in analyzing coded sera from healthy individuals.
- Except for the stipulation that HEp-2 cells should be used as substrate, each laboratory used its own in-house methodology so that the data might be expected to reflect the output of a cross-section of worldwide ANA reference laboratories.
- The sera were analyzed at 4 dilutions: 1:40, 1:80, 1:160, and 1:320.
- They found that in healthy individuals, the frequency of ANA did not differ significantly across the 4 age subgroups spanning 20-60 years of age.
- This putatively normal population was ANA positive in 31.7% of individuals at 1:40 serum dilution, 13.3% at 1:80, 5.0% at 1:160, and 3.3% at 1:320.

An interesting finding of this study was a remarkably higher incidence of "false" positive ANA's in patients with either a monoclonal gammopathy; or

with a myelodysplastic syndrome; this observation was attributed to the association of autoantibody with a "dysregulated" immune system at the bone marrow level.

Lightfoot has used Baysian calculation to determine that an individual with an ANA of 1:320 (and lacking other clinical criteria to suggest either SS or SLE) has less than a 1:100 chance in developing SLE or SS during a 5-year follow-up interval.

E. <u>MYTH</u>:

"SS Patients with "atypical antibody profiles" such as an ANA with anti-centromere pattern or a ANCA always represent overlap syndromes with other conditions such as Progressive Systemic Sclerosis (PSS) or Wegener's granulomatosus (WG)".

<u>MythBuster</u>: Although patients may develop an overlap syndrome with other autoimmune disorders such as PSS, the pattern of auto antibodies in patients with SS correlates more closely with their HLA-DR than with their clinical presentation[5, 6].

Ramos-Casals *et al*[7] studied 402 patients diagnosed with primary SS that had atypical antibodies including anti-centromere or ANCA.

- Patients with atypical auto-antibodies had no statistical differences extraglandular manifestations (except for a higher prevalence of Raynaud's phenomenon, 28% versus 7%),

F. *PEARL*:

MRI sialography can be used to visualize the ductal structure of the major salivary glands.

It is not necessary to perform a sialogram to assess the salivary status of SS patients or to visualize the ductal structures for punctual sialadenilits. This is important since most US academic centers do not have experience in retrograde sialography that is mentioned in diagnostic criteria and this invasive method may have morbidity if done by inexperienced radiologists or ENT.

MRI imaging of the parotid and submandibular glands has vastly improved[8]. If an MRI of the soft tissues of the neck is required (for example in a case of parotid gland swelling), then we ask for a gadolinium contrast study with "fat suppression" views that provides a nice evaluation of the glandular tissues[9, 10]. Although ultrasound of the glands has proven useful at certain

research centers (particularly in Europe), a great deal of experience is required to obtain reproducible results. As a result of readily available MRI imaging at most academic medical centers in the US, experience with ultrasound imaging of the glands has not been fully developed.

G. ***PEARL:***

Salivary flow rates can be evaluated by non- or minimally invasive methods.

This is important to correlate measurements of patient's symptoms with objective signs of dryness. Technicium scans of salivary function are performed after coating the tongue with a lemon concentrate[11-13]. The uptake of contrast material and its rate of secretion into the gland can be quantitated. Although the decreased flow rate is not specific to SS (i.e., many processes can contribute to decreased uptake or secretion), the method is useful in the evaluation of the patient who complains that "I don't feel any saliva in my mouth," but the oral mucosal tissues appear to be relatively intact. The finding of a normal Technicium scan should point the rheumatologist towards other causes of the patient's severe mouth complaints.

A recent study has studied "burning" mouth symptoms in a cohort of women in whom a diagnosis of SS could not be supported, even though they reported symptoms of dryness and taste disturbance. The authors suggested a local neuropathy or even psychogenic causes.

H. ***PEARL:***

There is significant variation when collecting saliva by oral expectoration or "sponge" methods[14, 15].

Simple expectorated saliva can be collected on a pre-weighed sponge placed under the tongue (called the Saxon test)[16]. However, there is significant variability in these measurements in the same patient over the course of the day or when measurements are repeated[14]. The reasons for the variability include:

- time since last meal
- last oral stimulation (including tooth brushing)
- history of smoking, as well as
- medications taken for other medical problems[17]

Although the variability in flow rates in both normal and SS is noted above, it is worth pointing out that the "normal salivary flow rate" for unstipulated

saliva from the parotid gland is 0.4 to 0.5 mL/min/gland. The normal flow rate for unstipulated, "resting" or "whole" saliva is 0.3 to 0.5 mol/min; for stimulated saliva, 1 to 2 mol/min. Values less than 0.1 mol/min are typically considered xerostomia, although reduced flow may not always be associated with complaints of dryness.

III. Myths and Pearls about CLINICAL PRESENTATIONS

A. ***PEARL:***

There is a close relationship between SS and a subset of patients with SLE[18].

Explain this to patients who may have particular concerns about the
The genetics, antibody profiles, and therapy of the subset of SLE patients with SS-A antibodies closely resemble that subset of SLE patients[19]. It has been suggested than many older patients diagnosed with "mild" SLE actually better fulfill the diagnosis of SS.[20] The relationship between 1*SS and a subset of SLE is shown schematically in Figure 8.

There are several "humorous" ways that our clinic has described SS. It has been suggested that SS is really SLE with only 4 criteria, due to the close

relationship in HLA-DR, autoantibodies and response to therapies[18, 21-23]. However, there are distinct differences in the patterns of disease involvement.

It might be more accurate to describe SS as having similar features as SLE but with "homing receptors" that yield:

1. *interstitial infiltrates* in salivary and lacrimal glands (that normally lack infiltrates),
2. *increased rates of lymphoma*,
3. *interstitial pneumonitis* (in contrast to pleurisy of SLE),
4. *interstitial nephritis* (in contrast to glomerulonephritis), and
5. *slightly different types of rashes* (such as hyperglobulinemia purpura)[24].

Thus, SS patients can have the same autoantibody and immune complex mediated complications as we find in SLE (i.e., ITP, hemolytic anemia, glomerulonephritis), but in the SS patient, our differential must include lymphocyte aggressive processes such as lymphocytic interstitial pneumonitis, mixed cryoglobulinemia, or lymphoma (Figure 2).

B. **MYTH:**

"There is a close relationship between lacrimal gland flow rates as measured by Schirmer's test and patient's symptoms of ocular dryness[25, 26]*."*

MythBuster: Tears do have an aqueous component, but also have proteins and *mucins that form a lubricating gel[27]. The tears have a different composition in terms of mucins, osmolality, and proteins than found in saliva. Also, the lipid component of the tears (secreted by the meibomian glands, discussed below) is important in retarding evaporation[25, 28-34].

When a patient describes "dry eyes," they are often referring to the increased viscosity as the upper lid tranverses the globe (shown schematically in Figures 3 and 4). Indeed, it has been suggested that the retention of a vital dye (such as Rose Bengal or fluorescein[25], shown schematically in Figure 5 and discussed below) is a reflection of this increased viscosity.

Thus, thus the volume of tears is determined by its aqueous content produced by the lacrimal gland, as well as the mucins[35] (esp. MUC4) produced by goblet cells of the ocular surface that contribute to the viscosity of the tear film[25, 27, 31, 35]. The number of goblet cells can be ascertained by

simple exfoliative cytology of the conjunctival surface or by conjunctival biopsy[36] (a method generally used in research or clinical trial settings).

C. ***PEARL:***

Patients may complain of dry eye, but their symptoms may also be due to increased evaporative loss associated with inflammation of the meiobian glands, a condition known as "blepharitis." [25, 27, 31, 35]

Of importance in normals, the tear film evaporation is retarded by a lipid layer produced by the meibonian glands (located at the edge of the eyelids) as shown schematically in Figures 6 and 7. The rate of evaporative loss depends on:

(a) *the lipid layer*,

(b) *the outside ambient humidity*, and

(c) *the blink rate* (discussed below), which determines the spreading.

Each of these factors may be important in treating the patient with dry or painful eyes.

The thickness of the lipid layer of the tear film in SS patients and the rate of evaporative loss of tears was increased in SS patients[37].

D. ***PEARL***:

There is a poor correlation of measurement of saliva and patient's complaints of dry mouth.

Unfortunately, there is a poor correlation between patients' descriptions of oral comfort and observed salivary flow rates[38-40]. This may reflect the misconception that saliva is "water" rather than a complicated mixture of water-proteins-mucins. This lubricating film provides a decreased viscosity for the oral mucosa and allows the tongue to more easily function during deglutition and talking[41].

In a recent report[42], reduced sulfating of mucin MUC5B was more closely linked to complaints of xerostomia in SS patients than aqueous water flow. Mucins are sulfated oligosaccharides that sequester water to provide lubrication and low viscosity of movement of the oral mucosa. They are familiar to many of us as the Lewis antigens that are secreted in saliva.

This defect in sulfating of MUC5B probably results from the inflammatory micro-environment due to release of cytokines and the disorganization of the

basal-lamina as a result of metalloproteinases that leads to dedifferentiation of acinar mucous cells[42].

E. ***PEARL:***

A dry mouth is not necessarily a painful mouth.

The physician should look for signs of oral candidiasis such as angular cheilitis or erythematous changes of the hard pallate, as well as lichen planus like changes in buccal recess[43].

Many patients have a dry mouth and this may be a normal part of the aging process[44, 45]. However, some event usually brings the patient to clinical attention. Frequently, a dry mouth is converted to a painful mouth by the ***occurrence of oral yeast infections,*** particularly in a patient who is on corticosteroids and has recently been taking antibiotics[46-48].

Alterations in the oral microbial flora, as well as relative decreases in the salivary flow of naturally occurring anti-fungal agents such as transferrin or calprotectin[49], histatins[50] and other small molecules of the defensin family[51] may further predispose the SS patient to oral candida[46-48]. A role for decreased level of anti-oxidants with these symptoms and the potential

exacerbating role of medications with anti-cholinergic side effects must always be considered[45, 52].

Daniels *et al* [43, 53, 54] has pointed out the importance of recognizing erythematous candidiasis, which presents as reddish petechiae frequently on the hard palate. It may be important for the patient to remove his/her denture in order to see the lesions. Also, lichen planus like lesions on the buccal mucosa (especially in the buccal recesses).

Treatment of the oral candidiasis may require a rather prolonged treated with topical anti-fungal drugs[41], using mouth rinses similar to those employed by the radiation therapists (often called XYZ mouth rinses) and topical application of nystatins[54].

F. ***PEARL:***

Changes in the microflora (and the biofilm surrounding the teeth) occur in the SS patient.

Even in the presence of excellent oral hygiene and routine care, an alteration of the oral microflora occurs. Almstaqh *et al*[55] noted 85% of the SS subjects had high numbers of mutans streptococci in addition to candida albican

species. This probably reflects changes in the "defensins and histatins" present in SS saliva[51], as well as pH changes and decreased ability of the tongue to remove debris from the mouth after eating.

G. ***PEARL:***

Burning mouth is a common complaint and may not be associated with a systemic autoimmune disorder such as SS.

Other causes of burning mouth syndrome must also be considered, including: ***nutritional deficiencies, hormonal changes associated with menopause, local oral infections, denture-related lesions, hypersensitivity reactions, medications, and systemic diseases including diabetes mellitus***[56]. In many cases, no clear cause can be found, and the dry mouth is attributed to a local neuropathy or to a manifestation of depression[45, 52].

Patton *et al*[57] reported a series of 45 patients with burning mouth in whom a diagnosis of SS (or above causes) could not be established. They suggested a localized neuropathy or psychogenic causes in these patients, and recommended a trial of topical clonazapam and anti-oxidants (alpha-lipoic acid) in some patients, and systemic agents used in neuropathy (gabapentin, pre-gabalin) or antidepressants with benefit in neuropathy (SSRI's, SNSRI's,

or NSRI's) in other patients. Agents with known anti-cholinergic side effects such as tricyclics were not tolerated.

H. **MYTH:**

"Complaints of dysphagia frequently are associated with motility disorders."

MythBuster: Subjective difficulty swallowing is one of the symptoms elicited in the diagnostic criteria for SS. A recent study using video-esophoscopy and manometry found that most of these patients had adequate mechanical deglutiton[58]. However, the decreased volume of saliva (pH 6-7.4) does not provide adequate "bulk" for swallowing, as well as diminished viscosity (due to mucins described above) or buffering capacity to neutralize basal gastric acidity in the lower esophagus or gastric antrum of SS patients[59, 60].

This imbalance due to decreased saliva volume and content predisposes to dysfunction of the gastro-esophageal sphincter, gastro-esophageal reflux and laryngo-tracheal reflux[59, 60]. The latter condition can be suspected when the patient engages in **repeated "throat clearing"** during the interview or has "unexplained" hoarseness. Of importance, the reflux of acid into the trachea

can stimulate the vagus nerve and mucus secretions, thus emulating symptoms from panic attack (choking) to sinus infections[59, 60].

I. **MYTH:**

"There is a close relationship between Schirmer's test and patients' complaints of ocular discomfort."

MythBuster: The poor correlation of "aqueous tear flow" and symptoms parallels the poor correlation noted in saliva aqueous flow and symptoms noted above. However, there are subtle but important differences between "tears" and "saliva" that will strongly impact the development of new therapies.

Macri and Plugfelder[25] recently correlated the fluorescein clearance test (FCT) and the Schirmer 1 test with the severity of corneal epithelial and eyelid disease in normal patients and patients with aqueous tear deficiency (ATD). The FCT showed stronger correlation with ocular irritation symptoms) and corneal fluorescein staining than the Schirmer 1 test. The combination of both FCT and Schirmer's I test improved the correlations with ocular irritation symptoms, corneal epithelial and eyelid pathologic signs, and corneal and conjunctival sensitivity.

J. ***PEARL:***

The incidence of demyelinating disorders is higher in SS than in the general population, but we really do not know how great is the risk[61].

Due to the recent availability of therapy for "continuous" progressive MS (i.e., Tsabri), this issue has therapeutic significance, and the need to counsel patients who are justifiably petrified by the concept of impending disability is critical.

The incidence of demyelating CNS lesions in SS appears elevated compared to the general population[61]. deSeze *et al* [62] recently estimated that up to 16% of MS patients have symptoms of dryness that can mimic SS in comparison to 5% of his "normal" population that exhibited sicca symptoms. However, only a small proportion of this group has abnormal salivary gland biopsies or antibodies against SS-A. Thus, the actual incidence of demyelinating disease remains unclear for several reasons and it is particularly unclear when neurological symptoms are the "presenting" clinical manifestation.

MRI scans of the brain have become very sensitive and findings of "non-specific spots" consistent with demyelination are often reported by the radiologist in patients in whom a clinical diagnosis of MS cannot be supported. These findings on MRI's of the brain are generally considered "non-specific" at our institution unless they are confirmed by characteristic other features of MS (such as VER, BAER, spinal tap), and can represent vascular lacunae (a normal variant).

K. ***PEARL:***

SS patients may also develop myelopathy and optic neuritis[63], similar to "Devic's disease" [64] in MS patients.

The therapeutic issue for the rheumatologist is whether this represents:

- **a central nervous system vasculitis** that might be treated with cytotoxic or biologic agents,
- OR whether this is the **start of progressive MS** that the neurologist may treat with high dose corticosteroids or biologic agents such as Tsabri, a monoclonal antibody that has been approved for "progressive" demyelinating disorder.

Initial studies on the correlation of MS and SS were complicated by the "ascertainment" bias of patients with sicca symptoms that were referred to institutions specializing in MS. Other centers pointed out that MS patients often exhibit dryness in the absence of positive salivary gland biopsies, leading to the suggestion that their dryness is due to central nervous involvement involving the cholinergic outflow tracts.

L. ***PEARL:***

SS patients may develop accelerated microvascular disease, similar to that recognized in SLE patients.

It has also recently been recognized that accelerated microvascular disease (discussed below), or sequellae of past ischemic events including migraine headaches may cause abnormalities on brain MRI. Thus, the differential diagnosis is important since entirely different types of therapies are required in each situation.

M. **MYTH:**

"A multiple sclerosis (MS) patient with a positive ANA has SS."

MythBuster: A common clinical question is whether the finding of ANA in a patient with an abnormal MRI means that the patient has CNS Sjögren's

syndrome. This question is difficult because positive ANA may be found in normal patients and in up to 20% of MS patients lacking other evidence of either SLE or SS[65, 66]. Also, patients with MS (and no evidence of SLE or SS) have an increased frequency of ANA.

N. ***PEARL:***

SS patients have more difficulty swallowing certain types of tablets or capsules than do other patients.

SS patients have deglutition problems due to dryness and lack of viscosity (associated with altered mucin production). As a result, they have difficulty with both swallowing and esophageal transit of many medications.

When possible, smaller "polished" tablets are preferred. An example is "branded" hydroxychloroquine (Plaquenil) that is a polished tablet, in comparison to many of the generics that are larger in size and contain a residue with bitter taste on the unpolished surface. Also, certain capsules (particularly large capsules containing iron replacement) may become adherent to the dry esophageal mucosal, where they may even cause erosion. For these reason, “polished” (coated) tablets are preferred to “sticky” capsules.

O. **MYTH:**

"The incidence of fibromyalgia in SS patients is the same as in the general population."

MythBuster: Giles and Isenberg[67] concluded that that "chronic fatigue" in SS patients was significantly higher than would be expected by simple co-existence of relatively common disorders. In fact, they noted a staggeringly high 50% of patients who noted fatigue as one of their chief complaints. The frequency of "fibromyalgia" or "chronic fatigue" was similar to SLE patients studied in the same region[67].

Since fibromyalgia is a symptom complex (rather than a single pathophysiologic entity defined by a specific pathogenetic event or biomarker), the frequency of "fibromyalgia" differs dramatically in different studies. This reflects both the stringency of the investigator in making the diagnosis and the cultural background of the patient population.

However, an increased frequency of "fibromyalgia" has been associated with both SS and SLE. In fact, the chronic fatigue and myalgias are such prevalent factors that they have made clinical drug development rather

difficult, since they are a large factor in the patient's evaluation of their "quality of life[3, 68-73].

It also should be noted that the clinical history of dryness in patients with fibromyalgia is similar to SS patients, but that they do not fulfill criteria for SS in that they lack objective ocular findings of KCS and have negative lip biopsies [74].

Perhaps the most intriguing group of patients with sicca symptoms are the reports in soldiers returning with "Gulf War Syndrome" where complaints such as fatigue, cognitive impairment, and odor intolerance have been attributed to various chemical exposures in the setting of stressful events[74].

P. ***PEARL:***

Risk factors for an earlier age of mortality in SS patients has not been clearly defined, but there are emerging concerns about cardiovascular factors[75].

The role of chronic inflammation as a factor in accelerated atherosclerotic disease as a risk factor for mortality is well established in SLE patients[76]. It is likely that similar factors are present in SS patients. Recently, a role of

small dense low-density lipoprotein (LDL) particles has been associated with atherosclerotic diseases in both SS and SLE patients[77]. Also of interest, specific autoantibodies against modified apo B-100 (within LDL), which appear to be related to human atherosclerotic disease, were reported in SS patients[77].

Thus, the rheumatologist must keep in mind traditional factors that predispose to cardiovascular disease (i.e., hypertension, lipid profiles, homocysteine) as well as antibodies to cardiolipin and lymphoma as important risk factors.

Q. ***PEARL:***

Thyroid disease is more frequent in SS patients.

The most common thyroid disorder found in association with SS was autoimmune thyroiditis, and the most common hormonal pattern was subclinical hypothyroidism[78]. pSS was ten times more frequent in patients with autoimmune thyroid disease, and autoimmune thyroiditis was nine times more frequent in pSS[78].

The coexistence of SS and thyroiditis is significantly more frequent and suggests a common genetic or environmental factor predisposition with similar pathogenic mechanisms[78, 79]. Therefore, SS should be studied in patients with thyroid disease and vice versa.

Antigens are shared by both thyroid and salivary glands, which could be responsible for the association between both diseases. Immunogenetic studies have suggested that both diseases have a common genetic predisposition. pSS and thyroid disease patients were mostly women with positive antithyroglobulin, anti-parietal cell and anti-thyroid peroxidase antibodies[78, 80].

R. ***PEARL:***

Autonomic Neuropathy is more frequent in SS patients. Many patients who describe "light-headed" symptoms may have this treatable cause so be sure to check supine and erect blood pressure and pulse.

In one recent study, autonomic neuropathy was more common among both SS and SLE patients [81]. Vagal dysfunction was established by applying three tests:

1. *Valsalva manoeuvre*,

2. *deep breathing test*, and

3. *heart rate response to standing*.

Sympathetic dysfunction was examined by applying two tests: blood pressure response to standing and handgrip test.

In all cardiovascular reflex tests, frequencies of abnormal results were significantly higher among the SS and SLE patients than among the controls [81].

In a separate recent study by Mandl *et al*[82], orthostatic test [acceleration index (AI)], orthostatic systolic and diastolic blood pressure response (lSBP ratio and lDBP ratio)], and finger skin blood flow test [vasoconstrictory (VAC) score] were reported to be more frequently abnormal in SS patients. It was important to note that the abnormalities did not correlate closely with Schirmer'[s test.

S. ***PEARL:***

Joint pain appears to be more frequent in SS women treated with aromatase inhibitors.

Women with breast cancer frequently receive adjuvant hormone therapy using aromatase inhibitors. With these treatments, joint pain is more

frequent in SS patients (30% to 40%) and quite often disabling (5% to 10%). This clinical observation complements recent observation of Sjogren-like syndromes occurring in aromatase knock-out mice.

T. ***PEARL:***

When SS occurs in males, look for other clinical stigmata of Klinefelter syndrome.

In some studies, up to 10% of SS patients are male[83]. In general, the clinical presentation, laboratory findings, extraglandular manifestations and minor salivary biopsies are similar to females with the slightly lower percent with a positive ANA and with higher percent exhibiting hematologic abnormalities[83].

In one study, up to 15% of the male SS patients had symptoms of Klinefelter's syndrome (lack of reproductive capacity, low testosterone, and abnormal XXY karyotype)[84].

These findings are interesting in view of the finding of translocation of a Toll 7 receptor in the BXSB mouse involving a portion of the X-chromosome to the Y-chromosome, since this is the only male mouse model to develop SS- or SLE-like features[85, 86].

U. ***PEARL:***

Pulmonary hypertension may develop in SS patients.

A recent study reviewed an unexpected 9 cases of PAH[87] in a cohort of 500 SS patients. The rheumatologist should make sure that the cardiac echo is performed (i.e., valves imaged) and interpretation being specifically read for PAH.

In the real world, cardiac echos are read as a "string" of different studies where the cardiologists are concentrating on left ventricular function (without recognizing that the ordering rheumatologist wanted information on PAH).

IV. Myths and Pearls about PATHOGENESIS

A. **MYTH:**

"Dryness in SS results from the total destruction of the gland."

MythBuster: In a lip biopsy from a SS patient with severe dryness, attention is usually focused on the dense lymphoid infiltrates (shown in Figure 9, frame A). However, it should be noted that residual acinar units are still visible (arrows).

Indeed, morphometric analysis has shown that only about 50% of the gland acinar or ductal tissue is replaced or destroyed[24, 88]. This may seem somewhat surprising, since a kidney or liver continue to function until their functional units are over 90% destroyed.

The interesting question is "why has the residual gland stopped functioning?" Kontinnen *et*[89] al have demonstrated that the glandular tissue (outside the lymphoid infiltrate) still has its neural innervation based on immunohistology[89]. Studies in man and murine models have indicated the presence of receptors for acetylcholine and other critical neurotransmitters[90-92]. It has been shown in animal models that the release of and response to neurotransmitters is strongly influenced by inflammatory cytokines including TNF and IL-1[93-95].

Further, the release of metalloproteinases in the inflammatory environment may interfere with the secretory gland's ability to maintain spatial orientation necessary to glandular function[96]. Recently, there has been increased interest in the potential role of antibodies directed against the muscarinic M3 receptor[97, 98].

B. ***PEARL:***

The environment plays a key role in exacerbating the patient's symptoms.

Although the patient has a *decreased* rate of aqueous tear formation and *increased* rate of evaporative loss due to the inflammatory process, each of these processes may be exacerbated by environmental factors.

Factors such as **low humidity** can be partially helped by humidifiers and the effect of dry winds by "wrap around" sunglasses or "side shields" on glasses. However, additional factors such as the **decreased "blink rate" associated with the use of computer monitors** is not usually appreciated.

Wolf *et al*[99] have pointed out that the modern work place environment is often an office with low humidity where individuals spent a great deal of the day staring at computer screens. Using cameras mounted on the computers, they could demonstrate a 90% decrease in the normal blink rate as the workers concentrated on their computer monitors. Thus, concentration on the "screen" can override the normal corneal surface conditions that lead to blinking and spreading of the available tears[100, 101]

C. ***PEARL:***

Antibody SS-A may play an integral role in the induction of SS and the type I IFN gene signature in salivary gland biopsies. This may help explain the relative failure of TNF antagonist therapies and lead the way to improved therapies.

Recent studies by Bave[102], Gottenberg[103, 104] and others have demonstrated that anti-SS A antibody complexed to the ribonucleoprotein complex (SS-A bound to hYRNA) can bind to Fcj receptors on plasmacytic dendritic cells. The internalized immune complex can then gain access to Toll receptors located in cytoplasmic vacuoles and stimulate production of type I IFN. (This is shown schematically in Figure 5). This model ties together the genetics (HLA-DR3 that is associated with production of anti-SS A antibodies) and the finding of activated plasmacytic dendritic cells that produce interferon type I. Thus, the contribution of the innate (HLA-DR independent) and acquired (HLA-DR dependent) pathways can be appreciated as potential targets (alone or in synergy) for therapy.

D. **MYTH:**

"The only problem with saliva is that the volume of flow is diminished."

MythBuster: Recent studies have compared the content of saliva in normals and in SS patients and shown significant differences in the profile of

proteins present as well as alteration in the post translational processing existing salivary proteins.

Normal saliva is the viscous, clear, watery fluid secreted from the parotid, submaxillary, sublingual and smaller mucous glands of the mouth. Saliva contains two major types of protein secretions:

1. a serous secretion containing the digestive enzyme ptyalin, and
2. a mucous secretion containing the lubricating aid ***mucin**.

The pH of saliva falls between 6 and 7.4. Saliva also contains large amounts of potassium and bicarbonate ions, and to a lesser extent sodium and chloride ions. In addition, saliva contains several antimicrobial constituents, including thiocyanate, lysozyme, immunoglobulins, lactoferrin and transferrin.

Mass spectrometry and expression microarray profiling have been used to identify candidate protein and mRNA biomarkers of primary SS[105]. Sixteen WS proteins were found to be down-regulated and twenty-five WS proteins were found to be up-regulated in primary SS patients compared with matched healthy control subjects.[105]

In a separate study, SS saliva showed significant alterations in post-translational modification of carbonic anhhydrase and the presence of proteins associated with oxidative stress injury[106].

Low salivary dehydroepiandrosterone and androgen-regulated cysteine-rich secretory protein 3 (crisp3) levels have recently been reported in saliva of SS patients.[107] This is important since it may help explain some of the hormonal influence on salivary function.

E. ***PEARL:***

The gene signature in the SS dry eye is associated with interferon gamma signature: This gene signature differs with the type I interferon signature noted in the glands (described above) and indicates the need for potentially treating both pathogenetic pathways.

As a result of the dryness, the ocular surface develops a form of squamous metaplasia, and conjunctival biopsies have demonstrated an interferon gamma gene signature[31]. This points out the difference between the type I interferon signature in the gland (described above) and the chronic inflammatory reaction on the ocular surface, as well as the potentially different requirements for therapy.

V. Myths and Pearls about TREATMENT

A. **MYTH:**

"TNF inhibitors have been shown to be beneficial in Sjögren's syndrome."

MythBuster: Although an initial pilot study suggested benefit of infliximab in SS[108], a larger multicenter study did not confirmed this initial observation[109]. Two studies have examined etanercept 25 mg twice weekly in SS [110, 111] for 12 weeks and these pilot studies did not report reduction in sicca symptoms or signs in SS. Also, treatment with Etanercept 25 mg twice weekly did not affect minor salivary gland biopsy results.

B. **MYTH:**

"Topical steroids should not be used in SS."

MythBuster: Pflugfelder et al[112] presented a randomized study in SS patients using Loteprednol 0.5% solution (Lotemax) or vehicle 4 times a day for 4 weeks. The patients, who had failed prior artificial tears, showed significant improvement and ability to return to traditional artificial tears after loteprednol. However, the use of steroid drops must always raise caution about glaucoma or cataracts, especially if the use if more prolonged.

D. ***PEARL:***

Salivary gland toxicity may accompany 131I treatment of thyroid disease.

Although not commonly appreciated, salivary gland toxicity may be an adverse effect of high-dose radioiodine (131I)[113]. A recent study of twenty patients revealed that 11 (15%) had symptoms of xerostomia within the first 48 hours, continuing for 12 months in seven of these patients. The onset of toxicity in a further nine (12%) patients with persistent symptoms did not occur until 3 months after therapy[113].

E. ***PEARL:***

The salivary gland biopsy of SS patients exhibit a gene signature of type I interferon. This may play an important role in determining the therapeutic agents most likely to be successful in trial.

Among the candidates for therapy may be Toll receptors, whose stimulation lead plasmacytic dendritic cells to release type I IFN. Expression of TLR2, TLR3, TLR4, and myeloid differentiation factor 88 (MyD88) in labial salivary glands has been demonstrated by immunohistochemistry[114]. Phosphorylation of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 (map kinase), Akt and activation of nuclear factor-kappaB (NF-kappaB) p65 have expression that is markedly increased

in the SS salivary gland. These activated genes were found in salivary-infiltrating mononuclear cells as well as acinar cells and ductal epithelial cells. These results suggest that TLR-mediated immune response in SS acts through the mitogen-activated protein kinase pathway[114].

Recently, Mannosoukos *et al*[115] have demonstrated the increased migration of plasmacytic dendritic cells into the gland and the resulting release of IL-12. This cytokine is known to bias T-cells towards traditional Th1 (release of interferon gamma) or the newly recognized T17 cell (which plays an active role in tissue destruction).

F. ***PEARL:***

Ask patients about their use of Chinese or other herbal medications.

Many patients do not inform their physicians about herbal drugs, as they consider them "nutritional" supplements. However, the agents may have significant direct toxicities on the SS patient, such as promoting profound hypokalemia in the SS patient with interstitial nephritis[116] or interaction with other 'western drugs." [117-121]

In our experience, the "herbal" medicines come in the form of "Chinese"

herbs or "Indian ayurvetic medicine." In addition to the adverse effect of the herb itself, the preparations may be contaminated with heavy metals (especially common in ayuvetic medications) or pesticides that were used at the time of crop harvesting. Obviously, these candidates can vary from lot to lot of the preparation, even with "scrupulous" and even more unpredictably with material obtained from "street" venders.

G. ***PEARL:***

Cosmetic procedures around the eye can exacerbate SS.

Three types of procedures come to mind:

1. **Lasik** surgery for the eye,
2. **Blepharoplasty** (eyelid "lift"), and
3. **Botox®** injection

Pre-existing SS is considered a ***definite contraindication* to lasik surgery**, due to the increased dryness after the procedure[122]. This increased dryness presumably results from the "flap" cut by the microtome across the cornea, which would be expected to sever the nerve bodies from afferent sensory nerves innervating the cornea. The resulting "neuropathic" eye is more sensitive to abrasions as well as to the sensation of dryness (friction as the upper lid traverses the globe).

Blepharoplasty may interrupt the basal tearing that occurs in the lower lid by the Glands of Sherring. This is because the stretching of the lid may disrupt the delicate neural interconnections within the network of glands. (These are the same glands that you stimulate when you massage your eyes). Another problem that we have encountered after blepharoplasty is increased zones of exposure keratitis. Particularly when sleeping, the lower lid may not make adequate contact with the upper lid, leading to a zone of increased evaporative loss and resulting dessicative injury.

Finally, a standard model for induction of keratoconjunctivitis sicca is Botox®[123].

H. ***PEARL:***

SS patients have unique and particular needs at the time of anesthesia and surgery.

Operating rooms typically have **low humidity** and patients are at risk for flare of their KCS or corneal abrasions. We have found this to be particularly true in the post-op recovery room, where the patient is partially awake with fluttering eyelids, receiving direct flow of oxygen (usually not

humidified) to the face, and not really aware of their eye symptoms as they awaken from anesthesia. Therefore, we recommend the use of ocular lubricants during surgery to prevent complications.

Also, the anesthesiologist must be careful with the amount of **anti-cholingergic agents** given during intubation, as the SS patient may be unduly sensitive and develop inspissated secretions that can not easily be cleared in the post-operative period (i.e., after abdominal or chest surgery) when raising tenacious secretions is difficult.

Finally, the use of **oral saliva substitutes** should be encouraged. It is expected that patients will be "NPO" (nothing by mouth) prior to many surgeries. In the absence of normal saliva, they will have unnecessary discomfort if they are not allowed to have their artificial saliva. We have found this particularly true when the patient is a "late in the day" case for elective procedures such as joint replacement.

I. ***PEARL:***

Anti-CD20 does more than simply deplete B-cells.

Anti-CD20 antibody therapy has recently been shown to have benefit on extraglandular manifestations of SS. The results for increased tear flow or saliva have been less dramatic and less consistent. However, double-blinded studies will be necessary before any conclusions on tearing can be drawn as the patients receive concurrent medications including corticosteroids.

As in SLE and RA, the best outcomes are associated with the emergence of Tregs in the circulation, identified by their marker CD25. It is likely that CD20 depletion affects the release of specific cytokines and growth factors from both B-cells and plasmacytic dendritic cells. As a result, the T-cell repertoire (both at the time of generation of new T-cells or the apoptosis of pre-existing T-cells may be biased in different pathways, including CD25 Tregs. Indeed, identification and optimization of factors that drive increased T-regs need to be identified.

J. ***PEARL:***

A wide range of peripheral neuropathies may be present in SS and constitute one of the most difficult aspects to treat.

Early attention to peripheral neuropathies is extremely important. The types of neuropathy include sensory including pure sensory and ganglionic neuronopathy. Sural nerve biopsy[124] frequently show vasculared or perivascular inflammation of small epineurial vessels (both arterioles and venules) and in some cases necrotizing vasculitis. Loss of myelinated nerve fibers was relatively common and loss of small diameter type I nerve fibers occurs.

Pathology in cases of sensory ganglioneuronopathy consists of loss of neuronal cell bodies and infiltration of T cells[124]. Also, peripheral motor neuropathies can include mono-neuritis multiplex (that derives from vasculitis) and CIPD ("chronic idiopathic peripheral demyelation") associated with anti-MAG (myelin associated glycoprpotein) disease. In addition, patients may suffer trigeminal and other cranial neuropathies, autonomic neuropathy, and mixed patterns of neuropathy[124].

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ganglioneuronopathy consists of loss of neuronal cell bodies and infiltration of T cells. Peripheral neuropathy in PSS often is refractory to treatment although newer biological agents may provide more effective treatment options.

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Table Captions

Tables

*Figures should be submitted as separate files