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Oral Health Strategy

Sjögren's Disease and systemic Lupus erythematosus: Manifestations and Management

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Outline

- SLE
 - Manifestations
 - Dental and Oral Management
- Sjögren's syndrome
 - Manifestations
 - Dental and Oral Management

SLE- Epidemiology

- Overall incidence
 - 1.0 (per 100,000) in Denmark to 8.7 in Brazil
- Overall prevalence
 - 28.3 in Denmark to 149.5 in Pennsylvania, USA
- UK studies: highest incidence and prevalence were reached by the Afro-Caribbean population
- US studies: the incidence and prevalence in African-Americans were 2-3 fold higher than European-Americans

ACR Criteria of Classification of SLE: 4/11

- Malar rash
- Discoid rash
- Photosensitivity (skin)
- Oral ulcers (oral or nasopharyngeal, usually painless)
- Arthritis (non-erosive)
- Serositis (pleuritis, pericarditis)
- Renal involvement (proteinuria, cellular casts)

ACR Criteria of Classification of SLE

- Neurologic disorder (seizures, psychosis)
- Hematologic disease (leukopenia, thrombocytopenia, lymphopenia)
- Immunologic disorder (lupus erythematosus [LE] cells; anti-dsDNA; anti-Smith [anti-Sm]; biologic false-positive [BFP] serologic test for syphilis [STS], antiphospholipid antibodies)
- ANA

Manifestations of SLE: Mucocutaneous

- Prevalence
 - 9 to 45% in systemic disease
 - 3 to 20% in localized cutaneous disease
- Presence of acute oral lesions may cause discomfort.
- Consider SLE or DLE in differential diagnosis of oral lesions.
- Dental Management: pain with mucosal manipulation in patients with acute exacerbation

Manifestations of SLE: Valvular Damage

- Mechanism for these vegetations is unclear
 - Likely a combination of immune complexes, complement activation and other inflammatory reactions, fibrosis, scarring and calcification
- 3.3 to 4.4 % of the SLE cohort had valvular problems according to transesophageal echocardiography (TTE)
- Use AHA recommended antibiotic prophylaxis for confirmed cardiac valvular disease.

Manifestations of SLE: Severe coronary atherosclerosis

- Prevalence 45%
- Evaluate blood pressure and coronary artery disease (CAD) symptoms (i.e. stable vs. unstable angina).
- Dental management
 - Consider anxiolytics
 - Defer treatment until medically stable for advanced CAD.

Manifestations of SLE: Renal Disease

- Prevalence: 50-67%
- Depending on the severity of renal disease, may require dialysis

Dental Management: Renal Disease

- Assess control of ESRD
 - Physician consult
 - Assess associated disease states
 - Laboratory Measures
 - Platelet Count
 - Hematocrit, Hemoglobin
 - BUN, Creatinine
- Increased attention for orofacial infections
- May be on chronic anticoagulant

Hemodialysis: Dental Management

- Dental treatment on non-hemodialysis days
- Consult with physician regarding antibiotic prophylaxis for hemoaccess site
- No BP side of access site

Kidney Disease: Medication Considerations

- Drugs excreted mainly by kidney
 - Tetracyclines, Aminoglycosides, Penicillins, Cephalosporins
 - Acyclovir
 - Ketoconazole
- Pain control
 - Acetaminophen may be safer than ASA, NSAIDs
 - Salicylates/NSAIDs may cause bleeding or fluid retention
 - Narcotics primarily metabolized in liver
 - Narcotics avoided with uremia

Kidney Disease: Medication Considerations

- Antibiotics
 - Clindamycin, Erythromycin, Metronidazole liver metabolism/elimination
 - Avoid aminoglycosides (e.g. streptomycin) and polymyxin B
 - Care with tetracycline and cephalosporins
 - Potassium containing penicillins: hyperkalemia in severe kidney disease: needs dialysis
- Frequency and dosages may require adjustment: Consult physician
 - Dependent on glomerular filtration rate

Manifestation of SLE: Neuropsychiatric

- Prevalence 67%
- For patients with seizures, review history and type of seizures. Protect patient from harm if has a seizure during therapy.
- For patients with psychoses, ensure adequate medical management of condition.

Manifestations of SLE: Hematologic disease

- The "penias" are secondary to peripheral destruction and not marrow suppression in SLE
- Autoimmune hemolytic anemia – in <10% of lupus patients
- Nonspecific anemia – 80% of patients
- Leukopenia – 50% of patients
- Thrombocytopenia – modest and severe

Dental Management

- Leukopenia
 - Evaluate lab values
 - Consider post-operative antibiotics for patients with ANC < 500
- Anemia of chronic disease
 - Evaluate lab values
 - Blood products with significant anemia (hemoglobin < 8.0)
- Thrombocytopenia
 - Obtain lab values and consider platelet transfusion for patients with severe thrombocytopenia (< 20,000)

Antiphospholipid Antibodies Syndrome

- Diagnosed by the presence of anticardiolipin antibodies or lupus anticoagulants and recurrent venous or arterial clotting
- The prevalence of APS is 14-20% in SLE patients, while SLE is diagnosed in 36% of APS patients
- Manifestations:
 - Deep venous thrombosis
 - Stroke
 - MI
 - Vasculopathies – vessel narrowing
 - Recurrent fetal loss due to placental insufficiency
- Management with ASA or warfarin therapy (INR – 3.0)

Aspirin withdrawal and risk of adverse cardiovascular event

- Patients with acute coronary syndrome who discontinued daily aspirin use are reported to have worse short-term outcomes than individuals not previously on aspirin therapy
 - 1358 patients admitted for suspected acute coronary syndrome (Collett et al.)
 - 930 nonusers of oral antiplatelet agents (OAA)
 - 355 prior users OAA
 - 73 recent withdrawers OAA (within 3 weeks before admission)
 - The recent withdrawers had higher 30 day rates of death or myocardial infarction 21.9% versus 12.4% than prior users
 - Five percent of the patients admitted with ACS had withdrawn OAA within 3 weeks before admission
 - It was concluded that prior users of OAA and patients with recent interruption of OAA displayed worse clinical outcomes than nonusers

Aspirin withdrawal and risk of adverse cardiovascular event

- 1236 patients hospitalized for ACS (Ferrari et al)
 - 51 (4.1%) had discontinued aspirin within one month of the ACS
 - Thirteen of these ACS cases were withdrawn from aspirin prior to a dental procedure
 - The mean delay between aspirin withdrawal and the acute coronary event was 10 ± 1.9 days (range 4-17 days)

Aspirin withdrawal and risk of adverse cardiovascular event

- 8688 patients who experienced first-time acute myocardial infarction (Fischer et al)
 - Risk of acute MI was 1.52 times greater for subjects who stopped NSAIDs (including aspirin) from 1 to 29 days compared with non-users
 - Risk was highest in subjects with rheumatoid arthritis or systemic lupus erythematosus (3.68 times higher than nonusers)
 - Current or past NSAID use (discontinued therapy ≥ 60 days prior to evaluation) was not associated with any increased risk of acute myocardial infarction

Minassian C. et al, Invasive dental treatment and risk of vascular events. *Ann Intern Med* 2010. Oct. 19;153:499-506.

- Discharge diagnosis of ischemic stroke or MI (n=1175) and exposed to invasive dental treatment
- Medicaid database
- 1-4 weeks after invasive procedure: incidence of vascular event 1.50 (1.09-2.06). Not significant for 4-24 weeks.
- Proposed explanation/mechanism
 - Increase in inflammation or bacteremia
 - Discontinuation of OTC antiplatelets, salicylates or NSAIDS prior to dental procedure (this information not collected in the database)

Manifestations of SLE: Increased infection risk

- Occurs in 14-100% of patients
- Immunosuppressive therapy
 - Increased risk of infection and healing post-operatively
- May have poor healing following invasive dental procedures. Evaluate closely post-operatively.

Manifestations of SLE: Secondary Sjögren's syndrome

- Secondary Sjögren's syndrome
- 7.5-30%
- Recent meta-analysis (Yaho, 2012) has highlighted that the prevalence of SS in SLE patients is estimated to be around 17.8%, and SS could be diagnosed in a period ranging from 0.33 to 10.8 years after the diagnosis of SLE.
- Increased incidence of caries and fungal infections.
- Dental Management- next section...

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SLE - Case

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- 32 y female with pain of cheeks
- Oral lesions present for 6 weeks
- Requires extraction of lower right 2nd molar related to extensive caries.
- PMH
 - SLE
 - Renal insufficiency
 - Antiphospholipid syndrome
- Meds
 - Coumadin

WBC	k/MM3	3.4-9.6	1.8
PMN	%	38-78	31
IgG	mg/dL	532-1482	1578
ANA			640
anti-dsDNA			Positive
anti-Sm			Positive
anti-SSA			Positive
anti-SSB			Negative
RBC	Mill/MM3	3.58-4.99	3.2
Hgb	g/DL	11.1-15	8.1
MCV	Cu Mcron	77-99	84
MCH	UUG	26-35	32
MHCH	g/DL	34-36	35.1
serum iron	micg/dL	50-150	110
Platelets	Thou/mm3	162-380	91

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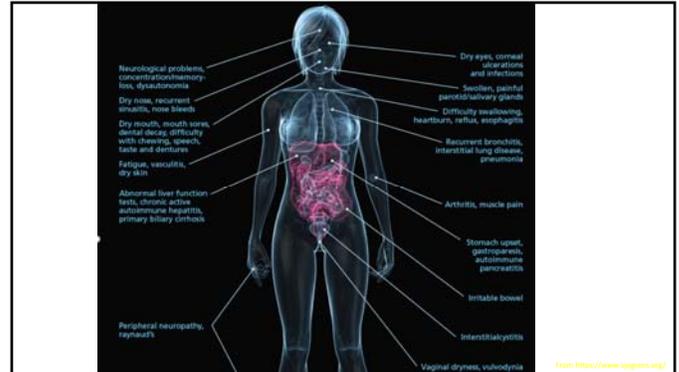
- Impact on dental management?
 - Low WBC/PMN
 - Autoimmune serology
 - Anemia
 - Low Platelets
 - Renal insufficiency
 - Warfarin

Sjögren's Syndrome

- The prevalence in the US: 2-4 million persons.
- Second most common rheumatic disease.
- Autoimmune exocrinopathy, characterized by dryness of the mouth and eyes resulting from a chronic, progressive loss of secretory function.
- F > M (9:1)
- Age: mid 50's

Sjögren's syndrome is a systemic disorder

- Primary SS: Salivary and lacrimal involvement
- Secondary SS: Salivary and/or lacrimal involvement plus another connective tissue disease
 - Associated connective tissue diseases include rheumatoid arthritis, systemic lupus erythematosus and scleroderma



SS- Neurological and Psychiatric Involvement

- Peripheral neuropathy presentations
 - Abnormal vibratory sensation
 - Paresthesias
 - Weakness
- CNS involvement can mimic multiple sclerosis
- Anxiety, depression, decreased QOL, impaired concentration

SS-Pulmonary Involvement

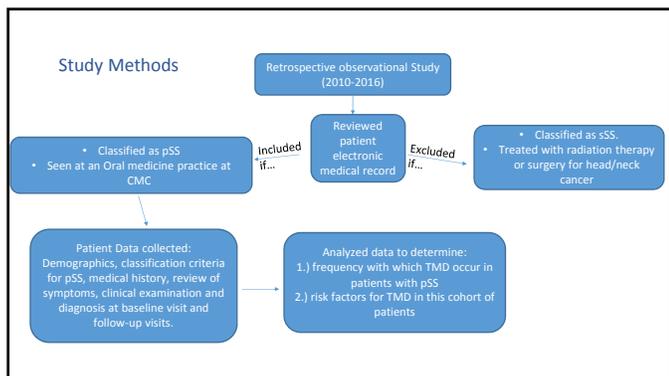
- Cough and dyspnea on exertion
- Lymphocytic interstitial pneumonitis
- Pulmonary involvement- 4 fold increase in mortality in 10 years comparing pSS with and without pulmonary involvement.

SS-Musculoskeletal Involvement

- Nonerosive arthritis in 40% of pSS
- Fibromyalgia in 20% of patients with pSS

Research Aims- TMD in SS

- Primary Aim:
 - Determine the prevalence of TMD in patients classified with primary Sjogren's syndrome.
- Secondary Aim:
 - Determine risk factors for TMD in this cohort of patients.



Inclusion Criteria

- Classified with pSS using the current classification criteria (ACR-EULAR)
- Met the diagnosis of TMD
- Had tenderness to palpation to the TMJ and/or muscles of mastication and/or neck muscles during clinical examination

The ACR/EULAR Classification Criteria for Primary Sjogren's Syndrome

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 focusses*	3
Anti-SSA/Ro positive	3
Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye	3
Schirmer test ≤ 5 mm/5 minutes in at least one eye	3
Unstimulated whole saliva flow rate ≤ 0.1 ml/minute	3

A score ≥ 4 classifies a patient who meets the inclusion criteria.
 * Ocular and/or oral dryness or suspicion of SjS according to EULAR SjS Disease Activity Index (ESSDAI) and does not have any of the exclusion criteria.
 - History of head and neck radiation, active HIV infection, AIDS, sarcoidosis, amyloidosis, graft-versus-host disease, IgG4-related disease.

Statistical Analysis and Results

- Analyses were performed using SAS Enterprise Guide version 6.1 (SAS Institute Inc., Cary, North Carolina, USA).
- Descriptive statistics: Prevalence determined by counts and frequencies

At baseline Visit

Variable (from clinical examination)	Count and Frequencies in this Cohort of patient
Diagnosis of TMD	63 (43.4%)
TTP on muscles of mastication	55 (37.9%)
TTP on neck muscles	39 (26.9%)
TTP of the TMJ	12 (8.3%)

Variable (patient reported)	Counts and frequencies
Oral burning	58 (40%)
Joint pain (one or more joint)	94 (64.8%)
Numbness and tingling (extremities)	56 (39.2%)
Raynaud's like symptoms	34 (23.78%)

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    graph TD
      A(145 Patients met the criteria) --> B(128 88.3% were females)
      A --> C(17 11.7% were males)
      A --> D(63 43.4% had TMD)
      D --> E(59 females)
      D --> F(4 males)
    
```

Statistical Analysis and Results

Univariate analyses (t tests and Chi-Square tests or non-parametric tests, when appropriate) were completed for pSS patients with TMD vs pSS without TMD

Variable	TMD N=63(43.4%)	NO TMD N=82(56.6%)	P value
Female	59 (93.7%)	69 (84.2%)	0.12
Age	55.83 ± 12.30	59.10 ± 12.08	0.11
Neurologic symptoms	32(50.8%)	24 (30.0%)	0.01
Fibromyalgia	14(22%)	6 (7.3%)	0.01
Osteoarthritis	20 (31.8%)	18 (22.0%)	0.18
Oral burning	28 (44.4%)	30 (36.6%)	0.33
Raynaud's phenomenon	16 (25.8%)	18 (22.2%)	0.61
Current smoking	5 (8.05%)	5 (6.33%)	0.69
Current Alcohol use	39 (61.9%)	48 (60.0%)	0.82
Joint pain symptoms	43 (68.25%)	51 (62.2%)	0.45
Positive Anti-SSA	19 (32.8%)	26 (33.3%)	0.94
Positive ANA	12 (20.7%)	21 (26.9%)	0.40
Recurrent swollen salivary glands	25 (39.7%)	24 (29.6%)	0.21
Unstimulated salivary flow (ml/15min)	1.20 ± 2.38	1.40 ± 1.83	0.58
Stimulated salivary flow (ml/15min)	4.96 ± 5.25	6.48 ± 5.84	0.11

Statistical Analysis and Results

- We identified 5 variables by univariate analysis to include in for multivariate logistic regression analysis with the outcome of TMD vs no TMD:
 - Sex, age, neurological symptoms, fibromyalgia and stimulated salivary flow
- Using backward elimination age was removed from the multivariate logistic regression model.
- Of significance, was the presence of :
 - fibromyalgia odds ratio (95% CI) = 3.13 (1.06 - 9.23),
 - neurologic complaints odds ratio (95% CI) = 2.8 (1.33 - 5.98)
 - female gender (95% CI) = 4.4 (1.08 -17.96)
 - stimulated salivary flow in ml/15 min (95% CI) = 0.93 (0.87- 0.99) (7% reduced odds of getting TMD symptoms)
- were associated with the presence of TMD symptoms in pSS patients after adjusting for other factors.
- With 1 ml increase in the stimulated salivary flow in 15 min there is 7% reduction in odds of getting TMD symptoms.

Conclusions

- 43% prevalence of temporomandibular disorders in patients with pSS.
- TMD was higher in pSS patients who have neurologic symptoms, fibromyalgia, female gender and in patient with low stimulated salivary flow.

Limitations

- Retrospective design
- Preliminary data

Future directions

- Prospective studies

SS- Vasculitis

- Prevalence between 5-10%
- One of the more significant EGM or SS with more severe consequences
 - Necrotizing vasculitis
 - Neurologic deficits
 - Chronic cutaneous ulcerations
 - Confers risk for non-Hodgkins lymphoma

Lymphoma and SS

- 44-fold increased risk of lymphoma in primary SS
 - SG / or extra-SG (80% MALT type)
- Meta Analysis Zintzaras, 2005
 - The 20 studies chosen for the analysis included 6 for SLE, 9 for RA, and 5 for pSS.
 - High risk of NHL development for pSS (random effects SIR, 18.8; 95% confidence interval [CI], 9.5-37.3);
 - Moderate risk for SLE (random effects SIR, 7.4; 95% CI, 3.3-17.0)
 - Lower risk for RA (random effects SIR, 3.9; 95% CI, 2.5-5.9). In
 - In RA, the random effects SIRs of NHL with conventional antirheumatic treatment, cytotoxic treatment, and treatment with a biological agent were 2.5 (95% CI, 0.7-9.0), 5.1 (95% CI, 0.9-28.6), and 11.5 (95% CI, 3.7-26.9), respectively.

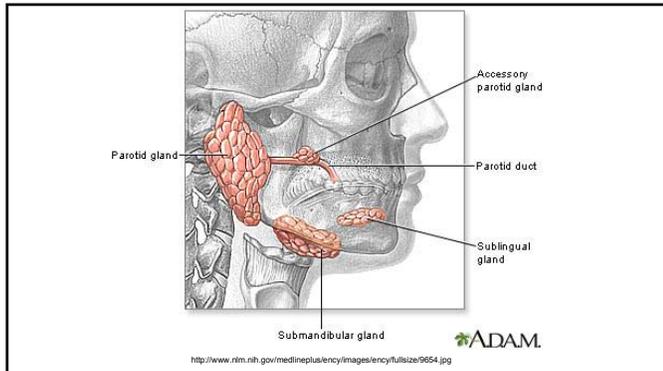
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Key Factor in Oral
Complications
Experienced in Sjögren's
is Salivary Hypofunction

Saliva

- Healthy adult produces 1.5 L of saliva in 24 hours.
- 3 major pairs of salivary glands
 - parotid
 - submandibular
 - sublingual
- Minor salivary glands
 - approximately 750
 - not located in the gingiva or anterior hard palate



Production of saliva

- Percentage of saliva production
 - Parotid 45%
 - Submandibular 45%
 - Sublingual 5%
 - Minor salivary glands 5%
- The sublingual and minor salivary glands produce the majority of mucous secretions.

Salivary Gland Physiology

Acinar cells initially secrete an isotonic fluid (140mEq/L NaCl)

contains 85% of the exocrine salivary proteins

As saliva passes through ductal tissue get reabsorption of NaCl

Results in a hypotonic (20mEq/L NaCl) saliva

Ductal cells contribute 15% of remaining salivary proteins

Salivary Gland Physiology

Autonomic control of secretion

- Parasympathetic stimulation responsible for secretory function
- Sympathetic stimulation responsible for protein secretion
- If block parasympathetic innervation, glandular atrophy occurs
- Blocking sympathetic innervation has little effect on the glands

Salivary gland hypofunction and xerostomia

• Definition

- Salivary gland hypofunction is a decrease in salivary secretion,
 - ≤ 0.1 ml/min for unstimulated whole salivary flow (<1.5 ml in 15 min)
 - ≤ 0.7 ml/min for stimulated whole salivary flow. (<10.5 ml in 15 min)
- Xerostomia is defined as the subjective complaint of dry mouth.

Causes of hyposalivation

Proposed mechanisms for hyposalivation include:

- Neurotransmitter receptor dysfunctions (e.g. Medications)
- Radiation-induced cellular DNA damage
- Salivary gland parenchymal destruction
- Immune dysregulation that may interfere with secretory processes
- Alterations of fluid and electrolytes (dehydration)
- Combinations of the above

ACR-EULAR Criteria For Primary Sjögren's Syndrome

Need to have complaint of oral or ocular dryness OR an extraglandular manifestation

- I. Schirmer's Test (+1)
- II. Ocular Staining (+1)
- III. Salivary Flow (+1)
- IV. Histopathology(+3)
- V. Anti-SSA (+3)

ACR-EULAR Criteria For Sjögren's Syndrome

Table 3. American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: The classification of primary Sjögren's syndrome applies to any individual who meets the inclusion criteria,^a does not have any of the conditions listed as exclusion criteria,[†] and has a score of ≥ 4 when the weights from the 5 criteria items below are summed.

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm ² ‡	3
Anti-SSA/Ro positive	3
Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye§	1
Schirmer's test ≤ 5 mm/5 minutes in at least 1 eye§	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/minute§#	1

Shiboski CH et al. Arthritis & Rheum 2016

Dryness Symptoms

I. Ocular Symptoms

1. Daily, persistent, troublesome dry eyes for >3 months?
2. Recurrent sensation of sand or gravel in eyes?
3. Use tear substitutes >3 times a day?

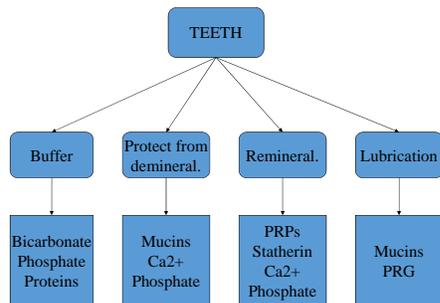
II. Oral Symptoms

1. Daily feeling of dry mouth for >3 months?
2. Recurrent or persistent swollen salivary glands?
3. Frequently drink liquids to ease swallowing?

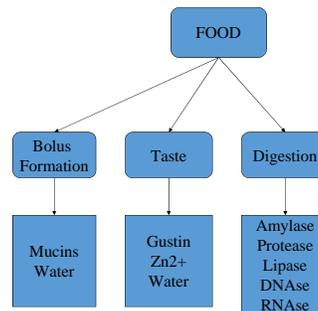
Extraglandular Manifestations

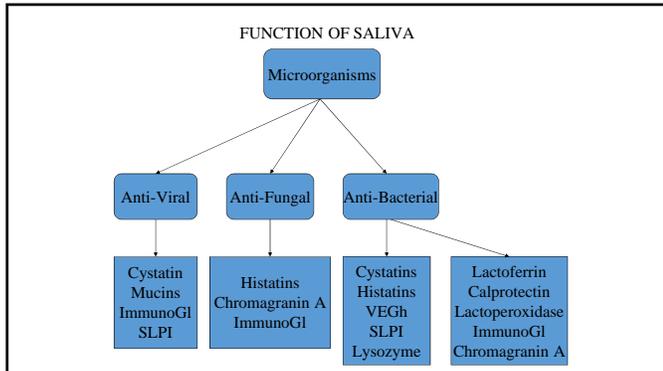
- Inflammation of other organ systems
 - Digestive system, kidneys, liver, lungs, thyroid, nervous system, BVs
- Signs/Symptoms
 - Fatigue
 - Muscle and joint pain
 - Nausea
 - Difficulty Swallowing
 - Heartburn
 - Cough
 - Numbness and tingling of extremities
 - Muscle weakness

FUNCTION OF SALIVA



FUNCTION OF SALIVA





Clinical Features of Salivary Gland Hypofunction in Sjögren's syndrome

- Oral hard and soft tissue signs
- Salivary signs
- Other signs

Sjögren's Syndrome Foundation (SSF): Clinical Practice Guidelines

- Systemic Management: Treatment of Inflammatory Musculoskeletal (MSK) Pain, Fatigue and Use of Biologics
- Oral Disease Management: Caries Prevention
- Ocular Manifestations of Sjögren's

Use of Fluoride

• Clinical Questions:

- In primary Sjögren's patients, does the use of a topical fluoride compared to no topical fluoride reduce the incidence, arrest or reverse coronal or root caries?
- In primary Sjögren's patients, is one topical fluoride agent more effective than another in reducing the incidence, or to arrest or reverse coronal or root caries?

• Recommendations:

- **Topical fluoride SHOULD BE USED** in Sjögren's patients with dry mouth.
- **No information was available to answer the second question.**

- **Strength of Recommendation:** This is a MODERATE Recommendation.

Salivary Stimulation

- **Clinical Question:**
 - In SS patients, does salivary stimulation compared to not stimulating saliva flow reduce the incidence, arrest or reverse coronal or root caries?
- **Recommendation:**
 - While no studies to-date link improved salivary function in SS pts to caries prevention, it is generally understood in the oral health community that **INCREASING SALIVA MAY CONTRIBUTE TO DECREASED CARIES INCIDENCE.**
 - Based on its expert opinion, the Topic Review Group **RECOMMENDS THAT SJOGREN'S PATIENTS WITH DRY MOUTH INCREASE SALIVA** through gustatory, masticatory stimulation, and pharmaceutical agents – For example, sugar-free lozenges and/or chewing gum, xylitol, mannitol, and the prescription medications pilocarpine and cevimeline.
- **Strength of Recommendation:** This is a WEAK Recommendation.

Antimicrobials

- **Clinical Question:**
 - In primary SS patients, does the use of antimicrobial agents compared to placebo reduce the incidence, arrest or reverse coronal or root caries?
- **Recommendation:**
 - **Chlorhexidine administered by varnish/gel/or rinse MAY BE CONSIDERED in Sjögren's patients with dry mouth and a high root caries rate.**
- **Strength of Recommendation:** This is a WEAK recommendation. Due to insufficient/weak evidence, this recommendation is based on expert opinion.

Non-fluoride remineralizing agents

- **Clinical Question:**
 - In pSS patients, does the use of non-fluoride remineralization agents compared to placebo reduce the incidence, arrest or reverse coronal or root caries?
 - In pSS patients, does the use of non-fluoride remineralization agents compared to the use of fluoride reduce the incidence, arrest or reverse coronal or root caries?
- **Recommendation:**
 - **Non-fluoride remineralizing agents MAY BE CONSIDERED as an adjunct therapy in Sjögren's patients with dry mouth and a high root caries rate.**
 - Insufficient information was available to answer the second question.
- **Strength of Recommendation:** This is a MODERATE Recommendation.

Soft tissue effects of salivary dysfunction in Sjögren's syndrome

- Mucosal dryness and atrophy
- Increased infections
 - fungal, bacterial
- Loss of papillation or furrowing of tongue

Study: Sjögren's Syndrome and Autoimmune Lesions

- We defined OLAIE as the presence of lesions upon clinical examination, which included: lichen planus; aphthous stomatitis; pemphigoid; pemphigus; linear IgA disease; chronic ulcerative stomatitis; or lesions of systemic connective tissue disease by immunofluorescence.

Results

- 155 patients diagnosed with primary SS: 52 from CMC, 55 from BCD and 48 from UF.
- The mean age was 59.9 years (SD±12.5)
- 140 (90.3%) were female.
- There were no differences in age between the 3 sites, but a higher percentage of women was identified at UF (98%) compared to CMC (87%) and BCD (87%) (p=0.005).

Results

- 19 patients with primary SS (12.3%) had OLAIE.
 - CMC reported 11 (21.2%)
 - BCD reported 4 (7.3%)
 - UF reported 4 (8.3%)
- OLAIE clinical diagnosis
 - Lichen planus in 11/19 (58%) patients with OLAIE
 - Aphthous stomatitis in 6 (32%)
 - Chronic ulcerative stomatitis in 1 (5%)
 - Systemic connective tissue disease by immunofluorescence in 1 (5%).

Sjögren's Syndrome and Autoimmune Lesions

- Group with OLAIE reported a higher prevalence of irritable bowel syndrome (IBS) than the group without (36.4% vs. 10.4%, p=0.03).
- We found no association between OLAIE and the following: positive lip biopsy; positive anti-SSA or ANA; salivary flow rates; medications; or other medical conditions.
- Primary SS had a 12% (range: 7.3%-21.2%) prevalence of OLAIE. This wide range in prevalence between enrollment sites most likely relates to the different screening protocols for oral dryness.

Salivary signs of salivary hypofunction

- Diminished secretions on palpation
- Thicker, opaque, or viscous secretions
- Recurrent salivary gland infection
- Enlarged salivary glands

Symptoms of salivary hypofunction

- Dryness when eating meals
- Difficulty swallowing dry foods
- A need to drink fluids when swallowing dry foods
- The impression of too little saliva

Oral Burning

- Many local or systemic conditions may be the underlying cause
 - Tissue trauma from decreased saliva lubrication
 - Parafunctional habits
 - Candidiasis
 - Hematinic deficiency
 - Uncontrolled diabetes?
 - CNS lesion
 - Contact sensitivity/allergy
 - Vesiculerosive disease (LP, pemphigoid, pemphigus)
- Burning mouth Syndrome (BMS)- diagnosis of elimination

Burning Mouth Syndrome

- The cause of BMS is unknown- related to a neuropathy.
 - More common perimenopausal women
- Management
 - Alpha lipoic acid 300 mg 2x/day
 - Benzodiazepines: Clonazepam (0.25 - 0.5mg)
 - Gabapentin (100-1800mg)

Study: Xerostomia and oral burning

- What is the prevalence of oral burning in patients with a complaint of dry mouth?
- What predicts the presence of a burning in dry mouth patients?
- A retrospective cohort study of patients with a complaint of dry mouth.
- Dictation notes and charts of patients meeting these criteria from January 2004 to June 2009.
- 952 new patient encounters were examined and 170 met the inclusion criteria.
 - Yes to at least one of the following questions: "Have you had a daily feeling of dry mouth for more than 3 months?" or "Do you frequently drink liquids to aid in swallowing dry foods?"
- Unstimulated and stimulated salivary flow
- Work up for Sjögren's syndrome when appropriate

Xerostomia and oral burning

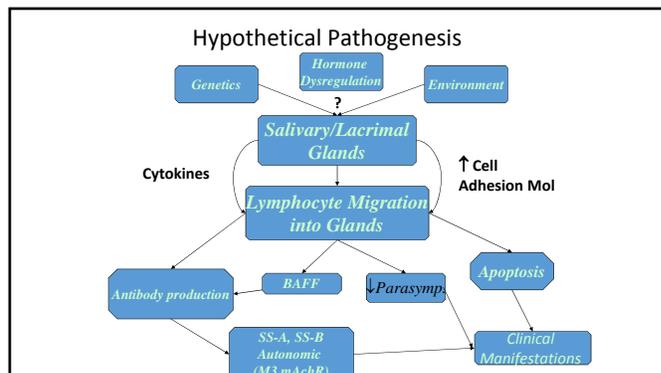
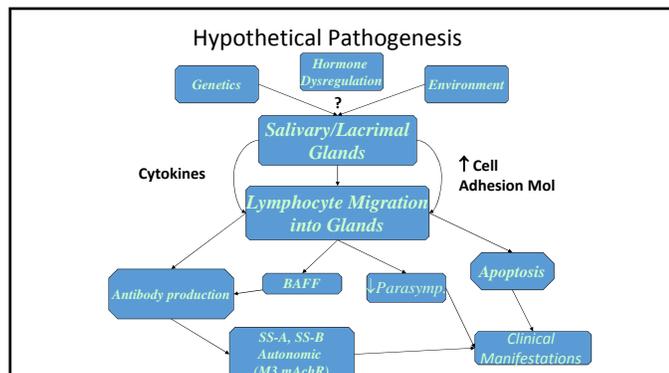
- Evaluated the following in multivariate analysis: age, gender, current smoking, removable prostheses, Sjögren's syndrome, stimulated saliva, taste disturbance, and herbal medication.
 - age (OR 1.03, CI 1.00-1.05, p=0.028) and use of herbal medications (OR 0.26, CI 0.10-0.67, p=0.005) were found to be significant.

Xerostomia and oral burning

- Some of herbal medications may be protective against burning
- It is also possible that herbal medications are not protective, but rather their use may be an alternative for xerostomic prescription medications that can precipitate a feeling of burning mouth.
- Fifty one (30%) had Sjögren's disease
 - 39 primary SS and 12 secondary SS.
 - Oral burning was identified in 23 (45%) of all SS patients

Rouleau TS, Shychuk AJ, Kayastha J, Lockhart PB, Nussbaum ML, Brennan MT. A retrospective, cohort study of the prevalence and risk factors of oral burning in patients with dry mouth. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011; Jun;111(6):720-5.

Management of Sjögren's Disease



Autonomic dysfunction

- FDA approved medications for dry mouth
 - Cevimeline (Evoxac®) 30 mg tid
 - Pilocarpine (Salagen®) 5 (7.5) mg qid
- Clinical trials have shown a similar benefit for dry eyes

Side effects are common with both pilocarpine and cevimeline due to widespread exocrine stimulation.

Sweating
Flushing
Urinary urgency
GI upset

Assessment of Residual Salivary Function

- Important to determine if stimulated flow is > than unstimulated flow
- Stimulated Flow > than unstimulated flow
 - Consider Salivary Stimulation
 - Start OTC- mechanical and gustatory stimulants
 - Not all patients will be able to tolerate frequent gum chewing as this may exacerbate temporomandibular disorder (TMD) symptoms.
 - If OTC insufficient: parasympathomimetics

Assessment of Residual Salivary Function

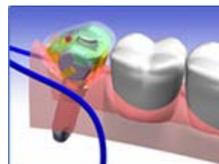
- Stimulated flow similar to Unstimulated Flow
 - Consider mucosal comfort Agents
 - Commercially available saliva substitutes containing thickening agents such as carboxymethyl cellulose and mucin are the most common.
 - Use of bedside humidifiers, particularly at night, may lessen discomfort due to oral dryness.

PRODUCTS FOR DRY MOUTH	
<p>SALIVA (dry) (Nucys Inc.) Customer Service: 1-877-478-2266 Website: www.saliva.com Lotion/gel spray/ointment/foam Available on-line and at CVS</p> <p>NIMORON (dry) (Alipha Pharmaceuticals) Customer Service: 1-813-398-8279 Website: www.alipha.com Lotion and liquid New prescription but needs a separate order and a pharmacy</p> <p>ORAMERIL (dry) (Cantone Health) Customer Service: 1-800-443-1443 Website: www.orameril.com Lotion/gel (spray/ointment) 3-4 times Virginia, CV</p> <p>ORALID (dry) (Gulfstream Oral Care) Customer Service: 1-800-898-2747 Website: www.oralid.com Spray and mouth rinse Virginia, TX, MA, FL, TN</p> <p>XYLIMELTY (dry) (OralHealth, Corp.) Customer Service: 1-877-872-6543 Website: www.xyylimelty.com Mouth rinse only On-line or at Your Ad Pharmacy</p> <p>MIRACETAL MEDICAL (dry) (HSD Laboratories) Customer Service: 1-800-851-4487 Website: www.miracetal.com Oral Rinse, Oral Spray, Lotion/gel On-line only</p> <p>EPIC (dry) (Eye Dental) Customer Service: 1-800-884-1742 Website: www.epicdental.com Spray/Gel, Mouth, Lotion/gel, and Rinse On-line only</p>	<p>BIOGEN PRODUCTS (dry) (BiochemHealthCare) Customer Service: 1-800-822-2254 Website: www.biogen.com Dry Mouth Treatment & Oral Care products Moisturizing Mouth Spray, Oral Rinse/Liquid, Dry Mouth Mouthwash, Oral Rinse Oral</p> <p>MIRACETAL PRODUCTS (dry) (Cantone) Customer Service: 1-800-443-1443 Website: www.cantone.com Gels, Lotion/gel, Spray, Mouthwash (several products) Available for purchase on-line</p> <p>ACT (dry) (Chaparral) Customer Service: 1-800-ACT-82388 Website: www.actoral.com Dry Mouth Rinse, Lotion/gel Oral Care Center</p> <p>StentorGel Oral Rinse (dry) (Stentor, Pharm.) Customer Service: (800) 963-8881 Website: www.stentor.com This experimental calcium phosphate resin is a prescription mouth rinse</p> <p>Fluores & Dry Mouth Products Customer Service: 1-888-842-8171 Website: www.fluores.com Helps dry mouth spray and ointment (dry) web site for more info</p> <p>Verano (dry) (Biochemetics Laboratory) Website: www.biochemetics.com Phone: (714) 444-6554 Mouthwash, Capsules, Gel, Toothpaste, Gels, Pastilles, Spray Available for purchase on-line or at CVS</p>

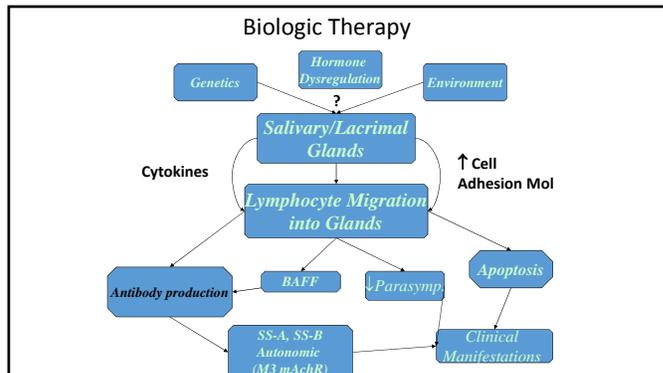
** This list is not all inclusive. Questions concerning the use of any product should be directed toward your doctor.

Oral Dryness

- Saliwell Device: Electrostimulation of nerves that control saliva
- Improvement in dryness



<http://www.saliwell.com>

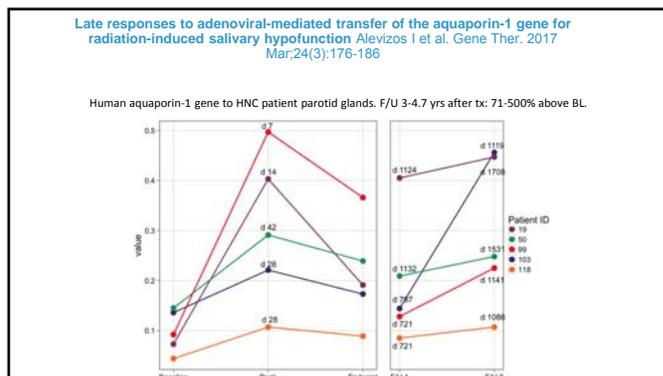


Biologics for SS

Table 1 - Summary of potential monoclonal antibodies for primary Sjögren's syndrome after [17].

Target	Name
B-cell markers	
CD20	Rituximab, Ocrelizumab, Afluzumab, Ibritumomab tiuxetan, Ofatumumab, TRU-015, Tositumomab, Velizumab
CD19	Tapitumomab pagtcox
CD22	Epratuzumab, Icotuzumab/ozogamicin
Other B-cell markers	Detumomab, Caliximab
Cytokines	
Bly/BAFF ± APR1	Belimumab, Atacept
IL-6	Tocilizumab, Etrasimomab, ALED18 IL-6 and Situximab
IL-12/IL-23	Brodalumab (ABT-874), Ustekinumab (NT0-1275)
Interferon-α	Etrasimomab, Sifalimumab
Interferon-γ	Fostolizumab
Adhesion molecules	
VCAM-1	S-11182
CD11/CD18	Efalizumab/Raptiva targeting CD11a, Erlezumab targeting CD18, Rozelezumab/LeukArrest (CD11/CD18)
Cell-cell interactions	
LFA-3/CD2	Abatacept
CD80/CD86/CD28/CTLA-4	Abatacept, Tremelimumab, Ipilimumab
CD40/CD154/CD40	Rapizumab (hu)SC8, BC9588, Antova), Toralizumab (DEC-131, 16640)

(Bowen, S et al. La Presse Medicale e495-e509, sept 2012)



New Treatment Guidelines for Sjögren's Disease. Rheum Dis Clin N America (2016);42; 531-551.

- <https://www.sjogrens.org/files/research/RheumatologyCPG.pdf>
- Oral Management for Caries
- Evaluation of Dry Eye
- Guideline for management of Dry eye based on cause and severity
- Extraoral and extraglandular manifestations of Sjögren's disease
- Guidelines of DMARDs for musculoskeletal pain in Sjögren's Disease
- Guidelines for treatment of fatigue
- Guidelines for biological medications in Sjögren's disease

Sjögren's Case

- This 56 year-old female is self-referred for the evaluation of Sjogren's syndrome and oral complications from dry mouth.
- History of Present Illness:
 - Symptoms started with dry eyes 2.5 yrs ago- progressively worsening. Restasis helps somewhat.
 - Dry mouth started 2 yrs ago and has also been progressive. Made better with Biotene spray. Worse with dry foods.
 - Recently saw her dentist and was told that she is having areas of decalcifications in her dentition and currently has a temporary crown.
 - Pt reports occasional burning sensations and is unsure if she has thrush. Symptoms especially with tongue (when eating) and gingiva (when brushing).
- Past Medical History
 - Hypertension, hypothyroid, alopecia, lichen planus (biopsy proven of skin 2009), osteoarthritis, constrictive bronchiolitis

Sjögren's Case

- Medications:
 - Lovoxyl, Cozaar, Salagen, Restasis, Centrum, Fish Oil, Clotrimazole/Bethameth, Pepcid, Loratadine, Ibuprofen, Tylenol
- NKDA
- Social History:
 - Patient denies tobacco. Denies alcohol use. Denies use of illicit drugs.
- Family History:
 - Dad deceased with arthritis and alzheimers, heart, lung, and thyroid problems. Mother with arthritis (not sure of type), brain aneurysm, and renal insufficiency. Brother and sister with hypertension and arthritis (not sure of type).
- Review of Systems:
 - Patient denies chest pain and difficulty breathing. Denies joint pain. Denies nausea, vomiting. Numbness and tingling of hands at night on occasion. Denies symptoms consistent with Raynaud's phenomenon. Fatigue for several years. Denies brain fog. Denies all other systemic abnormalities.

Sjögren's Case

- Extraoral: bilateral angular cheilitis and cracking of lips, TTP with right masseter (2/3), right temporalis (2/3) and right SCM 3/3. All other muscles of mastication, neck muscles or TMJs WNL. No LAD, so asymmetry.
- Intraoral:
 - Creamy white plaques of lower left vestibule and lower labial mucosa that can be wiped off.
 - Generalized upper facial erythema band measuring 2 - 4 mm. Lower facial erythema band measuring 2 - 4 mm.
 - Mild reticular pattern of left posterior buccal mucosa. Palatal erythema adjacent to upper right 2nd molar and upper left 2nd premolar and 1st molar.
 - Lateral borders of tongue bilaterally have papilla atrophy with erythema and white plaque type lesions and left side with mild reticular pattern.
 - Anterior half of tongue with plaque-type, erythematous areas.
 - Teeth intact, well restored. Scattered areas of decalcification at gingival margin.
 - Dry appearance of tissue, no saliva from all 4 major salivary glands.

Sjogren's Workup

- Ocular symptoms - Patient positive.
- Oral dryness symptoms - Patient was positive.
- Ocular signs - The Schirmer's I test for right eye was 0 mm in 5 minutes and the left eye was 0 mm in 5 minutes (stated by patient from one year ago): (+1)
- Salivary flow - The unstimulated salivary flow was 0 ml in 15 minutes. (+1)
 - Patient also had 0 ml stimulated saliva after 15 minutes. (+1)
- Autoantibodies - SSA positive (+3)
- Minor salivary gland biopsy - completed indicating a focus score of 12.0 (+3)

Problem List

- Meets primary SS classification
- Oral dryness and burning
- Bilateral angular cheilitis/dry, cracking lips and likely pseudomembranous candidiasis.
- Patient with evidence of intraoral lichen planus (biopsy?).
- TMD
- Decalcification at the gingival margin

Management strategy

- Primary SS: referral back to primary care (consideration of rheumatology consult)
- Oral dryness and burning:
 - Continue use of Biotene spray and discussed other dry mouth management techniques. D/C Salagen
- Fungal infection
 - Angular cheilitis: Nystatin/triamcinolone cream 4x/day until this clears (currently on Lortisone). Use aquaphor for her dry lips.
 - Pseudomembranous candidiasis: Clotrimazole troches (10 mg 5x/day for 7 days)

Management strategy

- Oral Lichen Planus
 - Clobetasol gel under occlusion and prevent a fungal infection by using concomitant clotrimazole troches 2x/day and probiotic yogurt 1x/day.
 - Consideration of biopsy to r/o dysplastic changes
- TMD
 - Flexeril 10 mg qhs x2 weeks, soft diet and warm compresses. Consideration of thin splint for parafunctional habits and PT.
- Decalcification
 - Gave prescription for Prevident. Encouraged closer F/U with her dentist (every 3-4 months)



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Questions?