Dry Mouth

Dr. Ross Kerr
ark3@nyu.edu
212-998-9885
Xerostomia

• The subjective experience of a dry mouth (ie a symptom)

Salivary Hypofunction

• The objective measurement of a reduction in salivary flow (a sign)
Clinical Aspects of Dry Mouth

I. Epidemiology of Dry Mouth
II. Saliva in Health
III. H&P and Diagnosis of Dry Mouth
IV. Causes of Dry Mouth
V. Dry Mouth and Oral Consequences
VI. Treatment of Dry Mouth
Average prevalence of xerostomia approximately 20%

- Highly variable prevalence across different studies
- Higher in women vs men
- Higher in the elderly (>30%)
- Highest in institutionalized elderly
- Higher if medical conditions/medication use
- Higher if compromised dental status
- Sjogren’s syndrome and head and neck radiation (almost 100%)

• Large older population “Baby-Boomers”
  – 2004: 23.5% >55yo (7.5 million)
  – ~1.5 million with xerostomia
• ~200,000 patients with Sjogren’s
• ~20,000 survivors of head and neck cancer who have received radiation treatment
Review

The functions of human saliva: A review sponsored by the World Workshop on Oral Medicine VI

C. Dawes a,+, A.M.L. Pedersen b, A. Villa c,d, J. Ekström e, G.B. Proctor f, A. Vissink g, D. Aframian h, R. McGowan i, A. Aliko j,1, N. Narayana k, Y.W. Sia l, R.K. Joshi m, S.B. Jensen b, A.R. Kerr n,i, A. Wolff o

a Department of Oral Biology, University of Manitoba, Canada
b Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
c Division of Oral Medicine and Dentistry, Brigham and Women’s Hospital, USA
d Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, USA
e Department of Pharmacology, The Sahlgrenska Academy, University of Gothenburg, Sweden
f Dental Institute, King’s College London, UK
g University of Groningen and University Medical Center Groningen, Department of Oral and Maxillofacial Surgery, The Netherlands
h The Hebrew University, Israel
i New York University, New York, USA
j Faculty of Dental Medicine, Tirana, Albania
k UNMC College of Dentistry, USA
l McGill University, Canada
m DAPMRV Dental College, Bangalore, India
n New York College of Dentistry, New York, USA
o Tel-Aviv Sourasky Medical Center and Saliwell Ltd., Israel
Role of Saliva in Health

- Moistening and lubrication
- Taste and smell
- Digestion
- Protection of the oral mucosa and esophagus
- Acquired enamel pellicle
- Salivary clearance
- Salivary inorganic components, erosion and dental caries
- Anti-bacterial, anti-viral, anti-fungal and some other effects of salivary proteins
- Wound-healing factors
Total production of 500-600ml/day
Saliva Composition

• Water makes up >99%
• Other constituents include:
  – Inorganic ions eg bicarbonate, Ca$^{2+}$, phosphate
  – Organic molecules
  – Macromolecules: proteins
• Influenced by numerous factors:
  – Gland source
  – Flow rate
  – Type/length of stimulation
  – Circadian rhythms
  – Others: diet, hormonal (pregnancy), exercise, drugs, various diseases, genetics
Proteins in Saliva

- Mucins (MUC5B and MUC7)
- Secretory immunoglobulins (IgA)
- Cystatins
- Histatins
- Lactoferrin
- Lysozyme
- Sialoperoxidase

- Amylases
- Lingual lipase
- Statherins
- Proline-rich proteins
- Agglutinin
- Defensins
- Cathelicidin
Unstimulated Saliva Production
300 ml/day

- Most important for overall oral comfort
- Flow rate: mean 0.3 ml/min
  - “Normal” range is very wide
  - Factors affecting unstimulated flow include:
    - Dehydration
    - Body posture
    - Lighting conditions
    - Circadian/circannual rhythm (lowest during sleep)
    - Medications
    - Age is an independent factor for whole saliva and submandibular/sublingual gland secretion.
Dry mouth may not be perceived until >50% of unstimulated salivary flow is lost.

Dawes C. J Dent Res. 1987
Stimulated Saliva Production
200+ ml/day

• Flow rate: mean 1-2 ml/min, maximum 7 ml/min
  – “Normal” range is very wide
  – Factors affecting stimulated flow include:
    • Mechanical stimuli
    • Vomiting
    • Gustatory/olfactory stimuli
      – Acid especially
    • Gland size
    • Age is an independent factor for whole saliva but not for parotid and minor gland secretions

_Percival RS, J Dent Res. 2004_
Parotids

- Serous secretion
- Exits through Stenson’s duct opening
- 20% of unstimulated volume
- 50% of stimulated volume
Submandibular Glands

- Mucous/serous secretion
- Exits through Wharton’s duct openings
- 65% of unstimulated volume
- 30% of stimulated volume
Sublingual & Minor Glands

• Sublingual gland secretions
  – Mucous (viscous)
  – 7-8% unstimulated flow

• Minor gland secretions
  – Mucous (very viscous)
  – 7-8% unstimulated flow
H&P and Diagnosis of Dry Mouth
Up to 25% of the general population may complain of dry mouth (> in elderly)

History of Dry Mouth

• Chief complaint=Dry mouth
• History of chief complaint
• Medical History
  – Medical conditions
  – Medications (prescription/OTC)
  – Review of systems
  – Family history
• Social History (habits eg tobacco/alcohol)
• Psychosocial status (Axis II)
• Dietary/nutritional history
• Dental/periodontal history
History of Chief Complaint

• Onset
• Differences during day
• Mouth-breather, humidity levels
  – oral evaporation
• Stress levels
• Oral vs non-oral symptoms
• Aggravating and relieving factors
Subjective Oral Symptoms

- Saliva: feels foamy, viscous, ropy
- Lips: dry, cracked
- Tongue: burning/pain
- Salivary glands: swollen, painful
- Thirst: frequent fluid intake, keep water at bedside
- Mastication: dry mouth when eating, difficulty using a denture
- Dysphagia: difficulty swallowing without fluids
- Speech: difficulty speaking (dysphonia)
- Taste: difficulty tasting (dysgeusia)
Subjective Symptoms: Review of Systems

• Throat: dryness, hoarseness, cough
• Nose: dryness, frequent crust formation, decrease in smell, congestion
• Eyes: dryness, gritty, burning, itching, blurred vision, photophobia
• Skin: dryness, flaky
• Joints: pain, swelling, stiffness
• GI: heartburn, constipation
• Vagina: dryness, burning, itching, dyspareunia, fungal infection history
• Others: fatigue, weakness, aching, weight loss, depression
Physical Examination

• Extra-Oral Examination
  – Facial assymetry, swelling of glands, skin (dryness, turgor)

• Intra-Oral Examination
  – Overall appearance of dryness (sublingual “pool”)
  – Quality of saliva (consistency/color)
  – Expression of saliva from orifices following palpation of major glands
  – Hard and soft-tissue abnormalities/pathology

• Salivary flow studies (sialometry)
  – Whole vs individual glands
  – Unstimulated vs stimulated
# The Challacombe Scale of Clinical Oral Dryness

The Challacombe Scale was developed from research conducted at King’s College London Dental Institute under the supervision of Professor Stephen Challacombe. The purpose of this scale is to be able to visually identify and quantify whether your patient has xerostomia (dry mouth) and if so, how it changes over time and the most appropriate therapy options. This scale is applicable whatever your profession.

The Challacombe Scale works as an additive score of 1 to 10: 1 being the least and 10 being the most severe. Each feature scores 1 and symptoms will not necessarily progress in the order shown, but summated scores indicate likely patient needs. Score changes over time can be used to monitor symptom progression or regression.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mirror sticks to buccal mucosa</td>
<td>An additive score of 1 - 3 indicates mild dryness. May not need treatment or management. Sugar-free chewing gum for 15 mins, twice daily and attention to hydration is needed. Many drugs will cause mild dryness. Routine checkup monitoring required.</td>
</tr>
<tr>
<td>2</td>
<td>Mirror sticks to tongue</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Saliva frothy</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No saliva pooling in floor of mouth</td>
<td>An additive score of 4 - 6 indicates moderate dryness. Sugar-free chewing gum or simple sialogogues may be required. Needs to be investigated further if reasons for dryness are not clear. Saliva substitutes and topical fluoride may be helpful. Monitor at regular intervals especially for early decay and symptom change.</td>
</tr>
<tr>
<td>5</td>
<td>Tongue shows generalised shortened papillae (mild depapillation)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Altered gingival architecture (ie. smooth)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Glassy appearance of oral mucosa, especially palate</td>
<td>An additive score of 7 - 10 indicates severe dryness. Saliva substitutes and topical fluoride usually needed. Cause of hyposalivation needs to be ascertained and Sjogren’s Syndrome excluded. Refer for investigation and diagnosis. Patients then need to be monitored for changing symptoms and signs, with possible further specialist input if worsening.</td>
</tr>
<tr>
<td>8</td>
<td>Tongue lobulated / fissured</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Corvical caries (more than two teeth)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Debris on palate or sticking to teeth</td>
<td></td>
</tr>
</tbody>
</table>
Simple In-Office Sialometry

- Graduated plastic tube (>10ml with 0.1ml divisions)
- Collect after overnight fast or >1.5hrs post prandial
- Quiet environment
- Unstimulated flow (USFR):
  - Seated, bow head, swallow, start clock, allow saliva to drip out of mouth for 5 mins, measure flow rate in ml/min
- Stimulated flow (if USF rate < 0.1-0.2ml/min):
  - Chew with flavorless gum base (+) or lemon-flavored candy (++), or challenge with pilocarpine (5mg/wait 30 mins) or cevimeline (30mg/wait 90mins)
Sialometry:

• Difficult to gauge since dependent upon patient’s normal baseline

• Abnormal flow rates:
  • Unstimulated flow rate <0.1-0.2 ml/min
  • Stimulated flow rate <0.5 ml/min

• Low flow rates possible in absence of symptoms (and vice versa)
Other Tests

- pH and buffering capacity
- Imaging: sialography, salivary scintigraphy
- Sialochemistry
- Labial/parotid biopsy
- Laboratory studies
Causes of Dry Mouth
Fig. 2. Salivary reflex secretion. Afferent stimuli are integrated in the primary salivary centres of the medulla. Autonomic parasympathetic efferent nerves conduct signals to salivary glands via parasympathetic ganglia situated near the target gland. Nerves project (lower broken line) from the medulla to the sympathetic centre in the upper thoracic segments of the spinal cord and from here sympathetic efferent nerves conduct signals to salivary glands via the superior cervical ganglion. Nerves project (upper broken line) from the cortex to the parasympathetic centres in the medulla and these can have an excitatory or inhibitory effect on salivary secretion. Efferent autonomic nerves stimulate salivary secretion and there is no peripheral inhibition of secretion via sympathetic nerves.
Parasympathetic stimulation produces copious saliva by all glands with variable protein concentration. Sympathetic stimulation produces less volume and generally higher protein concentration.
CNS: central nervous system, IP3: inositol triphosphate, DAG: diacyl-glycerol, VIP: vasoactive intestinal peptide, VPAC: VIP receptor, cAMP: cyclic adenosine monophosphate, cGMP: cyclic guanosine monophosphate, NO: nitric oxide
What causes dry mouth during anxiety?

- Central inhibition as a result of connections between the primary salivary centers and the higher centers of the brain.
- Normally, there is no peripheral inhibition of the salivary reflex (vasoconstriction by the sympathetic fibers is not part of the reflex)
Causes

• What causes xerostomia in absence of measurable salivary hypofunction?
  – May be a reduction in baseline sialometry which is still above “normal”
  – Saliva film thickness
    • Palatal mucous gland secretions?
    • Anterior dorsum of tongue?
  – Relative contributions by glands
    • Mucins, proteins?
  – Alterations in sensory perception?
  – Mental status/central inhibition?
Figure 1 Comparison of calculated thickness of the saliva film on anterior hard palate (AHP), buccal (BUC), anterior tongue (AT) and lower labial (LL) mucosal surfaces of patients complaining of dry mouth and control subjects. Flow rate from labial minor salivary glands is also compared. Dry mouth patients included those with primary and secondary Sjögrens syndrome, drug induced dryness, sialadenitis nodal osteoarthritis and xerostomia (SNOX) syndrome. All surfaces and minor salivary flow rate ($\mu l \ min^{-1} cm^{-2}$) showed significant reductions in dry mouth patients.
Causes: Salivary Hypofunction

- Dehydration
  \(\downarrow\) water intake, \(\uparrow\) water loss (eg DM, emesis)
- Medications (Rx & OTC)
- Direct damage to glands
  - Head and neck radiotherapy
  - Chemotherapy (reversible)
  - Autoimmune diseases
    - \(1^0\) vs \(2^0\) Sjögren’s Syndrome, GVHD
    - HIV disease
- Decreased mastication (tooth loss, soft diet)
- Conditions affecting the CNS:
  - psychologic disorders (depression/anxiety ?), Alzheimer’s, Parkinson’s, Cerebral palsy
- Others: Cystic fibrosis, renal, hepatic (HCV), thyroid diseases, sarcoidosis, sialadenitis nodal osteoarthritis and xerostomia (SNOX) syndrome
Medications

>500 drugs may be xerogenic

The incidence of xerostomia and SGH is correlated with the number of drugs taken, regardless of whether these drugs have an established association with dry mouth
Polypharmacy and Salivary Dysfunction

World Workshop on Oral Medicine
Meddry Group
Systematic Review on Medication-Induced Salivary Dysfunction
Fig. 2. WWOM VI group 1—Medication-Induced Salivary Gland Dysfunction. Front row (left to right): Ardita Aliko (Albania), Nagamani Narayana (USA), Anne Marie Pedersen (Denmark), Galit Almoznino (Israel), Ying Wai Sia (Canada), Siri Beier Jensen (Denmark). Back row (left to right): Doron Aframian (Israel), Revan Joshi (India), Ross Kerr (USA), Andy Wolff (Israel), Olufemi Oyetola (Nigeria), Alessandro Villa (USA), Arjan Vissink (The Netherlands), Colin Dawes (Canada). Not in photo: Jörgen Ekström (Sweden), Gordon Proctor (UK), Richard McGowan (USA).
The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD)

Purpose/Definition
The ATC/DDD system classifies therapeutic drugs. The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve quality of drug use.

Classification structure
In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified into five different levels. Drug consumption statistics (international and other levels) can be presented for each of these five levels.
Medication classes and established or proposed mechanisms of alterations of saliva production

<table>
<thead>
<tr>
<th>Medication (ATC code)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal agents (A03)</td>
<td>Block muscarinic receptors</td>
</tr>
<tr>
<td>Antiemetics (A04)</td>
<td>Block neurotransmitters dopamine D2, serotonin types 2-4 (5HT2-4), histamine type 1 (H1) and acetylcholine (muscarinic types M1-5) receptors</td>
</tr>
<tr>
<td>Antiobesity agents (A08)</td>
<td>Inhibit the neuronal uptake of norepinephrine, serotonin and dopamine in the central nervous system</td>
</tr>
<tr>
<td>Cardiovascular agents including antihypertensives and antiangrythmics (C02, C04 and C07)</td>
<td>Block muscarinic receptors and ( \alpha_1 ) and ( \beta_1 )-adrenergic receptors</td>
</tr>
<tr>
<td>Urologicals (G04)</td>
<td>Block muscarinic receptors and ( \alpha_1 )-adrenergic receptors</td>
</tr>
<tr>
<td>Muscle relaxants (M03)</td>
<td>Act as central ( \alpha_2 )-adrenergic receptors agonists</td>
</tr>
<tr>
<td>Analgesics (N02)</td>
<td>Inhibit the salivary reflex arc in the central nervous system by blocking noradrenaline reuptake</td>
</tr>
<tr>
<td>Antiepileptics (N03)</td>
<td>Act centrally by inducing a decrease in the release of neurotransmitters such as glutamate, norepinephrine, serotonin and dopamine</td>
</tr>
<tr>
<td>Category</td>
<td>Function Description</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Psycholeptics (N05)</td>
<td>Enhance GABA effect in the central nervous system; down-grade salivary secretory reflex; block muscarinic and α₁ and α₂ adrenergic receptors</td>
</tr>
<tr>
<td>Psychoanaleptics (N06)</td>
<td>Inhibit acetylcholinesterase; block serotonin, histamine, dopamine and norepinephrine reuptake</td>
</tr>
<tr>
<td>Agents for obstructive airway disease (R03)</td>
<td>Block muscarinic receptors M1 and M3</td>
</tr>
<tr>
<td>Antihistamines (R06)</td>
<td>Central inhibitory action on histamine 1-receptors and muscarinic receptors.</td>
</tr>
<tr>
<td>Ophthalmologicals (S01)</td>
<td>Inhibit acetylcholinesterase inhibitors and block α₂ adrenergic receptors</td>
</tr>
</tbody>
</table>

Head & Neck Radiotherapy

- 2+ Gy will cause temporary salivary dysfunction
- 26+ Gy will cause permanent salivary dysfunction
- Parotid more radiosensitive than submandibular
- Dose and field are critical
SJÖGREN’S SYNDROME

- Autoimmune exocrinopathy
- Dry mouth and eyes resulting from a chronic progressive loss of secretory function
- 2-4 million in US
- F > M (9:1)
- Age: mid 50’s
- Extraglandular manifestations: fatigue, lung, kidney, arthralgias, vasculitis, increased risk of lymphoma
• Primary SS: Salivary and lacrimal involvement
• Secondary SS: Salivary and/or lacrimal involvement plus another connective tissue disease
Table 7. Proposed classification criteria for SS*

The classification of SS, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least 2 of the following 3 objective features:
1. Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titer ≥1:320)
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm²†
3. Keratoconjunctivitis sicca with ocular staining score ≥3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)‡

Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:
- History of head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

* We excluded participants with rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or other connective tissue disease from these analyses since there were only 87 (6%) such participants. SS = Sjögren’s syndrome; ANA = antinuclear antibody.
† Using histopathologic definitions and focus score assessment methods as previously described (15).
‡ Using ocular staining score as previously described (17).
Courtesy of Dr. John Greenspan, UCSF
Dry Mouth and Oral Consequences
<table>
<thead>
<tr>
<th>Table V. Effects of long-standing xerostomia&lt;sup&gt;88-90&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased frequency of caries (particularly cervical caries)</td>
</tr>
<tr>
<td>Proclivity toward acute gingivitis</td>
</tr>
<tr>
<td>Dysarthria</td>
</tr>
<tr>
<td>Dysphagia</td>
</tr>
<tr>
<td>Dysgeusia</td>
</tr>
<tr>
<td>Proclivity toward candidal infection (eg, acute pseudomembranous candidiasis, median rhomboid glossitis, denture-associated stomatitis, angular cheilitis)</td>
</tr>
<tr>
<td>Burning tongue/depapillation of tongue</td>
</tr>
<tr>
<td>Oral mucosal soreness</td>
</tr>
<tr>
<td>Dry, sore, cracked lips</td>
</tr>
<tr>
<td>Salivary gland enlargement (various causes)</td>
</tr>
</tbody>
</table>

Porter et al OOOOE 97(1):2004
Caries

- Incipient decay
- Recurrent decay
- Coronal caries
- Root surface caries
Dysphagia

• Complaints of difficulty swallowing
• Increased duration of dry and wet swallows
• Increased risk of aspiration pneumonia
Dysgeusia

- Reduced enjoyment of eating
- Altered taste thresholds
- Exaggerated taste sensations
Candidiasis/Candidosis

- Angular cheilitis
- Erythematous
- Pseudomembranous
Denture Retention

- Decreased retention
- Decreased stability
- Increased complaints
- Increased risk of Candidal infections
Depapillated & Fissured Tongue
Other Mucosal Pathology

- Frictional keratoses
- Ulcerations
  - Traumatic
  - Aphthous ulcers
Others

• Retrograde salivary gland infections
• Sensitivity to spicy, acidic foods
• Erosion
• Halitosis
Treatment of Dry Mouth
1. To eliminate cause &/or improve signs and symptoms
2. To provide a higher quality of life
Do you have a diagnosis?

Did you perform the best possible evaluation?

3 Types of Patients with Xerostomia

<table>
<thead>
<tr>
<th>Unstimulated Flow Rate</th>
<th>Stimulated Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Improvement/Normal</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Abnormal Unstimulated (<0.1-0.2ml/min)
Abnormal Stimulated (<0.5ml/min)
1. If no measurable salivary hypofunction and no oral consequences:

- Normal flow has variability and there may be compositional abnormalities
- Perception of dry mouth may have a neurological component
- Salivary stimulation (OTC)
- Salivary lubrication
- Humidification
- Hydration/prevent dehydration (ie avoid alcohol, caffeine)
- Monitor closely to rule out emerging disease
2. If low USFR but responds to stimulation

- Look for possible causes
- Restore chewing function
- Reduce medication-induced salivary hypofunction
- Salivary stimulation OTC, Rx medications, others
- Salivary lubrication
- Humidification
- Hydration/prevent dehydration (ie avoid alcohol, caffeine)
- Treat oral consequences
Medication-Induced Salivary Hypofunction

- Coordinate with prescribing physician
- Reduce drugs with strong anticholinergic side-effects
- Reduce redundant drugs (e.g., multiple drugs for same indications)
- Change to less xerogenic medication
- Alter dose
- Reduce qhs dosages
- Alter administration time

Salivary stimulation?

- Masticatory stimuli
  - Harder diet, increase number of meals, sugarless chewing gum
- Gustatory stimuli (citric acid)
- Prescription Medications
- Electronic stimuli
- Acupuncture
OTC Salivary Stimulants
Sugarless Chewing Gum

• Increases flow rates. There is no good evidence that it may increase unstimulated flow rates following long-term use.

• Flow rates high for approx 10 mins until flavor and sweetness leach out, and only the gum base remains. However, gum base alone gives approx 2-3 times the unstimulated rate, so there is still benefit.

• Xylitol/sorbitol containing gums best for oral clearance.

Dawes C. Archives of Oral Biology 2004:49
Mucoadhesive Discs

- Contains a lubricating agent and citrus flavoring agent
- Lasts for 2-4 hours
- Increases subjective and objective measures of dry mouth

Kerr AR. JADA 2010;141;1250-1256
Prescription Medications

– Muscarinic agonists:
  • Pilocarpine 5-7.5mg tid & qhs (can go as high as 10mg qid)
  • Cevimeline 30mg tid (can go as high as 60mg tid)
  • Contraindications: significant cardiovascular, hepatic, renal or respiratory diseases, narrow angle glaucoma
  • Adverse effects >10%: sweating, flushing, rhinitis, increased urination, weakness

– Super-saturated calcium phosphate solution ???

RT: Mercadente V et al Oral Oncology 2017:66
SS: Ramos-Casals M et al JAMA 2010:304:4
Treatment of Sjogren’s Syndrome

Treatment of RT SGH

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Control Events</th>
<th>Total</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td><strong>Systemic Pilocarpine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson 1993</td>
<td>31</td>
<td>71</td>
<td>16</td>
<td>63</td>
<td>14.4%</td>
<td>2.28 [1.09, 4.75]</td>
<td></td>
</tr>
<tr>
<td>LeVeque 1993</td>
<td>32</td>
<td>69</td>
<td>20</td>
<td>77</td>
<td>16.2%</td>
<td>2.46 [1.23, 4.94]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>140</td>
<td>140</td>
<td></td>
<td>30.6%</td>
<td>2.37</td>
<td>[1.43, 3.94]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>63</td>
<td></td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity. Chi² = 0.02, df = 1 (P = 0.88); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.35 (P = 0.0008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Systemic Cevimeline** |                |       |                     |       |        |             |             |
| Chambers 2007          | 67             | 137   | 69                  | 145   | 35.8%  | 1.05 [0.66, 1.68] |             |
| Chambers 2007          | 65             | 137   | 48                  | 144   | 33.6%  | 1.81 [1.11, 2.92] |             |
| **Subtotal (95% CI)**  | 274            |       |                     |       | 69.4%  | 1.37 [0.98, 1.91] |             |
| Total events           | 132            |       | 117                 |       |        |             |             |
| Heterogeneity. Chi² = 2.47, df = 1 (P = 0.12); I² = 59% | | | | | | | |
| Test for overall effect: Z = 1.83 (P = 0.07) | | | | | | | |

Mercadente V et al Oral Oncology 66 (2017) 64–74
Biologics for SS: Conclusions

- Rituximab seems to preserve salivary gland function but does not seem to improve xerostomia (LoE 1A)
- Etanercept and infliximab does not seem to be effective in the management of pSS (LoE 2A)
- Abatacept and other anti-B cells therapies (belimumab and epratuzumab) should be further evaluated in RCTs (LoE 3A)
Hydration

- 64oz water/day or total weight divided by 2
- Avoid alcohol/caffeine
Electrical Stimulation

- SaliPen
- GenNarino

Strietzel FP et al. Oral Diseases 2007
Strietzel FP et al. Arthritis & Rheumatism 2011
Acupuncture

Low quality evidence
3. If the patient cannot respond to stimuli

- If dehydrated: rehydrate or treat underlying condition (eg DM)
- Salivary substitutes
- Minimizing damage to salivary glands
- Prevention and treatment of oral complications
- Future directions
Salivary Substitutes/Lubricating Agents: What’s the evidence?
36 RCTs involving 1597 participants met the inclusion criteria (27 studies explored salivary substitutes): 9 compared saliva substitutes to placebo, 18 compared two or more saliva substitutes. Only 1 trial had a low bias.

Oxygenated glycerol triester (OGT) saliva substitute spray shows evidence of effectiveness compared to an electrolyte spray (standardised mean difference (SMD) 0.77, 95% confidence interval (CI) 0.38 to 1.15) which corresponds to approximately a mean difference of 2 points on a 10-point visual analogue scale (VAS) for mouth dryness.

Both integrated mouthcare systems (toothpaste + gel + mouthwash) and oral reservoir devices show promising results but there is insufficient evidence at present to recommend their use.
A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact

S. B. Jensen · A. M. L. Pedersen · A. Vissink · E. Andersen · C. G. Brown · A. N. Davies · J. Dutilh · J. S. Fulton · L. Jankovic · N. N. F. Lopes · A. L. S. Mello · L. V. Muniz · C. A. Murdoch-Kinch · R. G. Nair · J. J. Napeñas · A. Nogueira-Rodrigues · D. Saunders · B. Stirling · I. von Bültzingslöwen · D. S. Weikel · L. S. Elting · E. K. L. Spijkervet · M. T. Brennan · Salivary Gland Hypofunction/Xerostomia Section · Oral Care Study Group · Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO)

Jensen SB et al. Supportive Care Cancer 2010:18
Xerostomia: MASCC/ISOO Guidelines

- The panel recommends the use of parotid sparing IMRT for prevention of salivary gland hypofunction and xerostomia in head and neck cancer patients (level of evidence II, recommendation grade A).

- No guideline possible for use of amifostine to prevent xerostomia during RT for head and neck cancer due to lack of consensus on the interpretation of existing evidence (level of evidence II, recommendation grade C).

- The panel recommends the use of oral pilocarpine following radiation therapy in head and neck cancer patients for improvement of xerostomia. The improvement of salivary gland hypofunction may be limited (level of evidence II, recommendation grade B).

- The panel cannot recommend the use of oral pilocarpine during radiotherapy in head and neck cancer patients for improvement of xerostomia as the results of the various randomized clinical trials were equivocal (level of evidence II, recommendation grade C).

- No guideline possible for use of gustatory and masticatory stimulation due to little evidence on which to base a guideline since this has been sparsely addressed specifically for patients suffering from xerostomia induced by cancer therapies (level of evidence III, recommendation grade D).
• The panel recommends the use of oral mucosal lubricants/saliva substitutes for short-term improvement of xerostomia following radiation therapy in head and neck cancer patients (level of evidence II, recommendation grade B).

• The panel suggests that the obtained level of sparing by submandibular salivary gland transfer might be of clinical significance (level of evidence IV, recommendation grade B).

• The panel suggests the use of acupuncture to stimulate salivary gland secretion and to alleviate xerostomia (level of evidence II, recommendation grade C).

• No guideline possible for hyperbaric oxygen treatment of xerostomia due to no evidence on which to base a guideline (level of evidence IV, recommendation grade D).

http://www.mascc.org/isoo-publications
Prevention and treatment of oral complications

- Close surveillance, regular recalls
- Optimal oral/denture hygiene
- Smooth off rough/sharp teeth/prostheses
- Restore dentition
- Avoidance of foods/beverages which exacerbate mucosal pain
- Caries
  - Fluoride therapy and restore
- Candidiasis
  - Institute antifungals (be aware of sugar content)
Topical Fluorides & Remineralizing Agents
The Future

NEXT EXIT
Photobiomodulation to prevent RT-induced SGH

FIG. 1. Salivary flow rates. Mean unstimulated salivary flow rates of patients treated with laser therapy and patients treated with clinical care only, at baseline (N0), at the 15th radiotherapy (RT) session (N15), at the last radiochemotherapy (RT-CT) session (Nf), and at 30 (N30) and 90 days (N90) after the end of oncologic treatment. (95% confidence intervals).

Gonnelli FAS et al. Photomedicine and Laser Surgery 2016:34;8
Poor Evidence for Rituximab Efficacy in Primary Sjogren’s Syndrome (Salivary Endpoints)

**Fig 4. Rituximab X Placebo.** Meta-analysis of the outcome salivary flow rate at week 24.

**Fig 5. Rituximab X Placebo.** Meta-analysis of the outcome oral dryness (VAS) at week 24.

Sialendoscopy-assisted treatment for chronic obstructive parotitis related to Sjogren syndrome

Yong-Feng Guo, MD, Ning-Ning Sun, MD, Chuan-Bin Wu, MS, Lei Xue, MD, and Qing Zhou, DDS, PhD

Objectives. Chronic obstructive parotitis related to Sjogren syndrome is not uncommon, but it is rarely reported in the literature. The aim of this study was to describe our experience in the treatment of chronic obstructive parotitis related to Sjogren syndrome.

Study Design. Seventeen cases of chronic obstructive parotitis related to Sjogren syndrome treated with sialendoscopy from June 2014 to June 2015 at the Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, were retrospectively reviewed. The cohort underwent ultrasonography, salivary gland scintigraphy, and sialography before sialendoscopy. All patients were asked to complete a visual analogue scale (VAS) evaluation before and 6 months after surgery. A paired t test was conducted, and \( P < .05 \) was considered statistically significant.

Results. The 17 study patients (27 parotid glands) successfully underwent interventional sialendoscopy under local anesthesia. The mean preoperative VAS score was 6, and the mean VAS score 6 months after sialendoscopy was significantly lower at 4.5 \( (P < .05) \).

Radiation-induced salivary hypofunction may become a thing of the past

Bruce J. Baum


Early responses to adenoviral-mediated transfer of the aquaporin-1 cDNA for radiation-induced salivary hypofunction

Bruce J. Baum\textsuperscript{a,}\textsuperscript{1}, Ilias Alevizos\textsuperscript{a}, Changyu Zheng\textsuperscript{a}, Ana P. Cotrim\textsuperscript{a}, Shuying Liu\textsuperscript{a}, Linda McCullagh\textsuperscript{a}, Corinne M. Goldsmith\textsuperscript{a}, Peter D. Burbelo\textsuperscript{b}, Deborah E. Citrin\textsuperscript{c}, James B. Mitchell\textsuperscript{d}, Liesl K. Nottingham\textsuperscript{e}, Susan F. Rudy\textsuperscript{g}, Carter Van Waes\textsuperscript{g}, Millie A. Whatley\textsuperscript{f}, Jaime S. Brahim\textsuperscript{g}, John A. Chiorini\textsuperscript{a}, Stamatina Danielides\textsuperscript{a}, R. James Turner\textsuperscript{a}, Nicholas J. Patronas\textsuperscript{h}, Clara C. Chen\textsuperscript{f}, Nikolay P. Nikolov\textsuperscript{a}, and Gabor G. Illei\textsuperscript{a}

\textsuperscript{a}Molecular Physiology and Therapeutics Branch, and \textsuperscript{b}Neurobiology and Pain Therapeutics Section, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892; \textsuperscript{c}Radiation Oncology Branch and \textsuperscript{d}Radiation Biology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; \textsuperscript{e}Head and Neck Surgery Branch, National Institute of Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD 20892; \textsuperscript{f}Nuclear Medicine Section and \textsuperscript{g}Section on Neuroradiology, Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD 20892; and \textsuperscript{h}Department of Oral-Maxillofacial Surgery, University of Maryland, Baltimore, MD 21201

Phase 1 trial showing safety and promising initial results

Case 1
74 yo female presents with a complaint of a dry mouth over the last 3 months and most recently she has been experiencing some oral burning and taste changes. She was referred by a dermatologist who thought she had a “glossodynia” and prescribed her amitriptyline which isn’t helping. She has a history of asthma (for which she currently she takes montelukast and a budesonide/formoterol inhaler daily), severe nasal polyps (she cannot breathe easily through her nose), hypothyroidism controlled with levothyroxine, GERD controlled with pantoprazole. She has never smoked and drinks 2-3 glasses of wine a day. The examination reveals no lymphadenopathy. There are no obvious carious lesions. There is a lack of salivary pooling in the floor of mouth. Your dental mirror sticks to the buccal mucosae. See the two images for the other intra-oral findings. The unstimulated flow rate (USFR) is 0.1ml/min. Following the examination the patient is given a sugar-free dry-mouth lozenge which generates an increase in salivary flow (equivalent to a stimulated flow rate (SFR) of 0.6ml/min).
Which of the following best characterizes this patient? Select a single response.

1. Normal USFR, normal SFR
2. Abnormal USFR, improvement/normal SFR
3. Abnormal USFR, abnormal SFR
4. Sjogren’s syndrome
5. Burning mouth syndrome
Which of the following best characterizes this patient? Select a single response.

1. Normal USFR, normal SFR
2. Abnormal USFR, improvement/normal SFR
3. Abnormal USFR, abnormal SFR
4. Sjogren’s syndrome
5. Burning mouth syndrome
Which of the following is the LEAST likely direct or indirect cause for the erythematous area involving the hard palate?

1. Amitriptyline use
2. Budesonide/formeterol inhaler use
3. Alcohol intake
4. Mouth breathing due to nasal polyps
5. GERD
Which of the following is the LEAST likely direct or indirect cause for the erythematous area involving the hard palate?

1. Amitriptyline use
2. Budesonide/formeterol inhaler use
3. Alcohol intake
4. Mouth breathing due to nasal polyps
5. GERD
Which of the following would be NOT be prudent in the management of this patient’s oral symptoms?

1. Recommend a change in her asthma medication
2. Recommend discontinuation of the amitriptyline
3. Prescribe over the counter sialogogues (ie gum/lozenges)
4. Prescribe a topical antifungal agent
5. Hydrate and avoid excessive alcohol and caffeine.
Which of the following would be NOT be prudent in the management of this patient’s oral symptoms?

1. **Recommend a change in her asthma medication**
2. Recommend discontinuation of the amitriptyline
3. Prescribe over the counter sialogogues (ie gum/lozenges)
4. Prescribe a topical antifungal agent
5. Hydrate and avoid excessive alcohol and caffeine.
Case 2
This 49 year old caucasian female presents with a chronic sore on the left side of her tongue (>1 month). She thinks she bit it during the night and despite her best intentions she continues to reinjure it. Her mouth is extremely dry and she has to take frequent sips of water during the day. Her medical history is complex. She had undergone multiple surgeries on her spine from herniated discs and is in constant pain (she takes MS Contin (slow release morphine), gabapentin, tizanidine and cyclobenzaprine). She is depressed (takes buproprion and sertraline), and has GERD (takes omeprazole). She currently smokes 5 cigarettes a day (10 pack year history). She has had three new restorations placed in the last 6 months due to recurrent caries. Her examination reveals no lymphadenopathy. Intraorally, you note her mouth is dry with a lack of salivary pooling in the floor of her mouth. The tongue is soft to palpation and there are some geographic lesions on the dorsal surface.
Which of the following is the LEAST likely to be linked directly to her dry mouth (ie risk factors)?

1. Morphine
2. Sertraline
3. Buproprion
4. Omeprazole
5. Cyclobenzaprine
Which of the following is the LEAST likely to be linked directly to her dry mouth (ie risk factors)?

1. Morphine
2. Sertraline
3. Bupropion
4. Omeprazole
5. Cyclobenzaprine
Your clinical diagnosis for the ulcer is traumatic.

Which of the following would NOT be part of the INITIAL management plan for this patient?

1. Use of saliva substitutes
2. Fluoride treatment (eg prescription fluoride varnish)
3. Discussing xerogenic medications with her physician
4. Fabrication of a night guard
5. A trial of cevimeline 5mg tid
Your clinical diagnosis for the ulcer is traumatic.

Which of the following would NOT be part of the INITIAL management plan for this patient?

1. Use of saliva substitutes
2. Fluoride treatment (eg prescription fluoride varnish)
3. Discussing xerogenic medications with her physician
4. Fabrication of a night guard
5. A trial of cevimeline 5mg tid
Case 2
This 45 year old African American female presents with dry mouth secondary to intensity modulated radiation treatment for a stage IV tonsillar cancer in 2010. There are no other medical issues. She can chew her food well but needs to drink water to help her swallow. She is particularly dry at night. Chewing gum helps a little to relieve her dryness.
Based on the images provided, which of the following signs suggest(s) she has a dry mouth? CHOOSE ALL POSSIBLE ANSWERS

1. Frothy saliva
2. Ropey saliva
3. Cervical enamel discoloration/hypopcalcification
4. Class V caries
5. Class VI caries
Based on the images provided, which of the following signs suggest(s) she has a dry mouth? CHOOSE ALL POSSIBLE ANSWERS

1. Frothy saliva
2. Ropey saliva
3. Cervical enamel discoloration/hypoplasticity
4. Class V caries
5. Class VI caries
Assuming all the salivary glands received a similar dose of radiation, in general which of the salivary glands are MOST sensitive to radiation treatment?

1. Sublingual
2. Parotids
3. Minor glands
4. Submandibular
5. Sublingual and minor glands
Assuming all the salivary glands received a similar dose of radiation, in general which of the salivary glands are MOST sensitive to radiation treatment?

1. Sublingual
2. **Parotids**
3. Minor glands
4. Submandibular
5. Sublingual and minor glands
Which of the following would NOT be part of the management plan for this patient?

1. Saliva substitutes
2. Fluoride treatment
3. Humidifying the bedroom
4. Pilocarpine or cevimeline
5. Gene therapy
Which of the following would NOT be part of the management plan for this patient?

1. Saliva substitutes
2. Fluoride treatment
3. Humidifying the bedroom
4. Pilocarpine or cevimeline
5. Gene therapy