

SALIVARY GLANDS AND SALIVA

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Diagnosing, managing, and preventing salivary gland disorders

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Introduction

Salivary function provides host protection, assists in the initiation of food and fluid intake, and enables communication through speech. Without adequate salivary output, oral and pharyngeal health declines along with a person's quality of life. The complaint of a dry mouth (xerostomia) and the objective finding of salivary dysfunction are common occurrences in older individuals, producing transient and permanent oral and systemic problems. Salivary dysfunction, however, is not a normal consequence of growing older, and is due to systemic diseases, medications, and head and neck radiotherapy. Diagnosis of salivary disorders begins with a careful medical history, head, and neck examination. While complaints of xerostomia may be indicative of a salivary gland disorder, salivary diseases can present without symptoms. Therefore, routine examination of salivary function must be part of any head, neck, and oral examination. Therapies are designed to prevent the development of oral and pharyngeal sequelae of salivary hypofunction. Current xerostomia-based treatments include replacement therapies and gustatory, masticatory, and pharmacological stimulants. Healthcare professionals can play a vital role in identifying patients at risk for developing salivary dysfunction, and should provide appropriate preventative and interven-

tive techniques that will help preserve a person's health, function, and quality of life.

Subjective complaints of xerostomia

The prevalence of xerostomia and salivary gland disorders is difficult to ascertain because of methodological differences in study populations and diagnostic criteria. The majority of patients treated for salivary disorders are those with Sjögren's syndrome (SS), adults being treated for head and neck cancer and those taking medications with antisialogogue sequelae. Combining these populations, the prevalence of xerostomia increases with age, and is probably ~30% of the population aged 65+ years (Ship, Pillemer and Baum, 2002).

Frequent oral symptoms of dry mouth are associated with mealtime. These complaints include altered taste; difficulty in eating, chewing, and swallowing, particularly dry foods; impaired eating without drinking accompanying liquids; and insufficient retention of or poorly fitting removable prostheses. Patients also complain of halitosis, a chronic burning sensation (stomatodynia) and intolerance to spicy foods that can affect the quality of a person's life (Fox *et al*, 1985; Mandel, 1989; Atkinson and Wu, 1994). These problems can lead to changes in food and fluid selection that may compromise nutritional status. They also can lead to choking, as well as an increased susceptibility to aspiration pneumonia, with consequent colonization of the lungs with gram-negative anaerobes from the gingival sulcus (Gibson and Barrett, 1992; Terpenning *et al*, 1993; Loesche *et al*, 1995). Xerostomia complaints at night-time are common, as salivary output normally reaches its lowest circadian levels during sleep (Dawes, 1975). These latter problems may be exacerbated by diminished oral motor tone leading to increased mouth breathing.

Many older adults experience salivary gland dysfunction and complain of xerostomia (Locker, 1993; Narhi, 1994; Thomson *et al*, 1999). While it was previously thought that salivary function declined with greater age,

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it is now accepted that output from major salivary glands does not undergo clinically significant decrements in healthy individuals (Baum, 1981; Heft and Baum, 1984; Ship and Baum, 1990; Challacombe, Percival and Marsh, 1995; Ship, Nolan and Puckett, 1995; Vissink *et al.*, 1996). Salivary constituents also appear to be age-stable in the absence of major medical problems and medications (Wu *et al.*, 1993; Rayment *et al.*, 2000). It is likely that numerous medical conditions and their treatments (medications, head and neck radiation, chemotherapy) contribute significantly to salivary gland dysfunction in the elderly (Mandel, 1980; Atkinson and Fox, 1992; Wu and Ship, 1993; Atkinson and Wu, 1994; Sreebny and Schwartz, 1997). Secretory reserve of salivary glands has been postulated to become diminished with increased age (Scott, Flower and Burns, 1987; Baum, Ship and Wu, 1992; Patel, Ghezzi and Ship, 2001), which may account for the greater prevalence of salivary disorders in the elderly, especially those taking medications. Further, biting forces have been correlated with salivary flow rates, and as biting forces may diminish with age, these may also play a role in the prevalence of xerostomia in the elderly (Yeh *et al.*, 2000).

Diagnosis of salivary gland disorders

Oral sequelae of salivary dysfunction

The extra and intraoral examination of the patient with salivary dysfunction will yield numerous hard and soft tissue signs. Extraoral findings include dry and cracked lips that are frequently colonized with *Candida* species (angular cheilitis). Visible enlargement of the major salivary glands may occur in patients with viral infections (mumps), salivary obstructions (secondary to salivary hypofunction), and SS. Some older adults develop an acute parotitis after undergoing extended periods of dehydration and general anesthesia. A swollen parotid gland can displace the earlobe and extend inferiorly over

the angle of the mandible. Medial to the posterior-inferior border of the mandible, a submandibular salivary gland swelling can be palpated. The glands may or may not be tender, and swelling is often recurrent (distinguishing it from mumps).

Intraoral findings of salivary gland dysfunction may range from subtle to obvious. The tongue becomes furrowed, desiccated, and sticky. Dry oral mucosal tissues become susceptible to trauma; oral mucositis leads to pain and increased likelihood of developing microbial infections. Palpation of the parotid papilla (at Stenson's duct) reveals little or no salivary output, whereas in the presence of a parotitis, palpation will yield suppurative material. Examination of the floor of the mouth (at Wharton's duct) often reveals decreased or absent saliva pooling. Oropharyngeal swallowing difficulties are best evaluated by ultrasound studies. Food bolus formation and translocation can be perturbed in patients with reduced salivary output.

One of the most common infections in patients with salivary dysfunction is oral candidiasis (e.g. Cannon and Chaffin, 1999). This fungal infection manifests itself as angular cheilitis of the lips, erythematous candidiasis beneath prostheses, and pseudomembranous candidiasis as a white plaque that can be removed from all oral mucosal surfaces. A second frequent infection is new and recurrent dental caries. Recurrent carious lesions are particularly common among today's elderly, because of the high prevalence of retained natural teeth and previously restored dental surfaces (Shay, 1997).

Edentulous and partially edentulous adults using removable prosthetic devices have diminished denture retention, which will impact adversely chewing, swallowing, speech, and nutritional intake (Ettinger, 1997). Denture-supporting mucosal tissues become friable and susceptible to traumatic lesions, further impairing use of removable prostheses. Speech and eating difficulties can impair social interactions and may cause some patients to avoid social engagements.

Table 1 Subjective measures of xerostomia

Measure	Response	Reference
Do you have difficulties swallowing any foods?	Yes/no	(Fox <i>et al.</i> , 1987)
Does your mouth feel dry when eating a meal?	Yes/no	(Fox <i>et al.</i> , 1987)
Do you sip liquids to aid in swallowing dry foods?	Yes/no	(Fox <i>et al.</i> , 1987)
Does the amount of saliva in your mouth seem to be too little, too much, or you don't notice it?	Yes/no	(Fox <i>et al.</i> , 1987)
Rate the difficulty you experience in speaking because of dryness	0–10 scale ^a	(Pai <i>et al.</i> , 2001)
Rate the difficulty you experience in swallowing because of dryness	0–10 scale ^a	(Pai <i>et al.</i> , 2001)
Rate how much saliva is in your mouth	0–10 scale ^b	(Pai <i>et al.</i> , 2001)
Rate the dryness of your mouth	0–10 scale ^c	(Pai <i>et al.</i> , 2001)
Rate the dryness of your throat	0–10 scale ^c	(Pai <i>et al.</i> , 2001)
Rate the dryness of your lips	0–10 scale ^c	(Pai <i>et al.</i> , 2001)
Rate the dryness of your tongue	0–10 scale ^c	(Pai <i>et al.</i> , 2001)
Rate the level of your thirst	0–10 scale ^d	(Pai <i>et al.</i> , 2001)
Dryness of lips	Present/absent	(Navazesh <i>et al.</i> , 1992)
Dryness of buccal mucosa	Present/absent	(Navazesh <i>et al.</i> , 1992)

^aFrom 'not difficult at all' to 'very difficult'

^bFrom 'a lot' to 'none'

^cFrom 'not dry at all' to 'very dry'

^dFrom 'not thirsty at all' to 'very thirsty'

Use of xerostomia questionnaires

Several scientifically validated questionnaires (Table 1) have been designed specifically for assessing salivary disorders and xerostomia, and may be helpful in clinical practice (Fox, Busch and Baum, 1987; Pai, Ghezzi and Ship, 2001). The majority of questions relate to xerostomia experienced during mealtime, and therefore these items may be most useful. Salivary hypofunction has also been predicted by four additional measures: dryness of lips, dryness of buccal mucosa, absence of saliva produced by gland palpation, and total decayed-missing-filled-teeth (DMFT) (Navazesh, Christensen and Brightman, 1992).

Collection of saliva

Numerous investigators have attempted to define the lower limits of 'normal' salivary flow rates. However, there is substantial variability in flow rates that makes it difficult to define diagnostically useful ranges of glandular fluid production. In studies of healthy persons across the lifespan, resting (unstimulated) fluid secretion varies 10–100-fold, while stimulated secretion varies 10–20-fold (Baum, 1981; Heft and Baum, 1984; Ship, Fox and Baum, 1991). Unstimulated secretions are probably more indicative of dry mouth complaints compared with stimulated secretions (Wang *et al*, 1998). Recent research data suggest that values below 45% of normal levels could be used to define salivary hypofunction (Ghezzi, Lange and Ship, 2000). It is also generally accepted that when an individual's glandular fluid production is decreased by about 50%, a person will begin to experience symptoms of oral dryness (Dawes, 1987). The best strategy is to simply monitor a patient's salivary health (both objectively and subjectively) over time (Ship *et al*, 1991).

The composition of saliva also exhibits considerable variability (Rudney, 1995). While salivary exocrine

proteins are critical for oral physiological performance, there are no common disease situations resulting in the deficiency of any single major salivary protein. Therefore, there is no practical reason to monitor the protein composition of a patient's saliva.

Biopsies, imaging and culturing

Intraoral and extraoral salivary gland swellings should be evaluated using histopathological and imaging techniques, depending upon the clinical scenario. Minor salivary gland mucoceles can undergo excisional biopsies, whereas larger tumors will benefit from incisional biopsies for histopathologic diagnosis and tumor staging in order to plan subsequent therapies (Golden and Hooley, 1994). Sialograms can identify changes in the salivary gland architecture, and are useful for major salivary gland swellings (Stiller *et al*, 1999). They are performed with radio-opaque iodine and extraoral radiographs (lateral cephalograms, panographs). Radioactive isotope scintiscans (e.g. T⁹⁹ pertechnetate) can provide a qualitative functional assessment of the major salivary glands (Kohn *et al*, 1992; Saito *et al*, 1997; Malpani, Jaiswar and Samuel, 1999). Magnetic resonance imaging and computerized tomography (CT) scans will help rule out salivary gland tumors and other pathoses associated with the craniofacial region that may adversely affect salivation. All salivary gland infections should be cultured to identify organisms that may be resistant to commonly used antibiotics.

Salivary gland infections, tumors and neoplasms

There are three classifications of intraoral sources of salivary gland diseases (infectious, non-infectious and neoplastic; Table 2) that must be considered in the diagnostic process of examining a patient with salivary dysfunction (Norman and Mitchell, 1998). Bacterial infections are more common in older persons

Table 2 Identifying salivary gland diseases

Pathology	Etiology
Infectious Acute sialadenitis Chronic recurrent sialadenitis Viral sialadenitis Non-infectious Sialectasis Sialolithiasis Sialadenosis Mucous cyst Mucocele Benign tumors Pleomorphic adenoma Monomorphic adenoma Malignant tumors Adenoid cystic carcinoma Mucoepidermoid carcinoma Acinic cell carcinoma Malignant mixed tumor ^a	Salivary hypofunction: secondary to dehydration, debilitation, medications Bacterial species: <i>Staphylococcus aureus</i> , <i>S. pyogenes</i> , <i>Streptococcus pneumoniae</i> , <i>Escherichia coli</i> Bacterial species (see acute sialadenitis) Paramyxovirus, Cytomegalovirus Salivary hypofunction: secondary to dehydration and postgeneral anesthesia Salivary hypofunction: secondary to dehydration, debilitation, medications, metabolic disorders, poor oral hygiene Malnutrition, alcoholic cirrhosis, diabetes mellitus, hyperlipidemia Blockage of an excretory duct Traumatic severance of a minor salivary gland duct, producing spillage of mucin into surrounding connective tissue

^aCarcinoma arising in a pleomorphic adenoma, and squamous cell carcinoma

who experience salivary hypofunction secondary to medications, head and neck radiation, systemic diseases, or dehydration (Almstahl and Wikstrom, 1999; Almstahl *et al*, 1999). Acute parotitis was commonly seen before the antibiotic era in terminally ill and dehydrated patients and contributed to mortality by sepsis. Now, acute parotitis is observed infrequently. Chronic parotitis is not unusual, and it follows obstruction of a major salivary gland duct with subsequent bacterial colonization and infection. Signs and symptoms of bacterial salivary infections include swelling, purulence from the major salivary gland duct, and pain (August *et al*, 1996).

Viral infections occur in persons of all ages, particularly in immunocompromised patients, and preferentially involve parotid glands. Mumps is caused by paramyxovirus, and presents as bilateral parotid gland swellings in children. Cytomegalovirus infections tend to be mild with non-specific findings, and are observed primarily in adults.

Non-infectious (reactive) causes of salivary diseases are most common because of obstruction of a salivary gland excretory duct, and can be divided into acute and chronic conditions. Acute sialadenitis usually results from an immediate partial or complete ductal obstruction (i.e. sialolithiasis), whereas chronic recurrent sialadenitis occurs as a result of prior infection and/or ductal scarring (Williams, Connor and Edmondson, 2000).

Mucoceleles are the most common reactive lesion of the lower lip, and are caused by local trauma. When a minor salivary gland duct is severed, mucin leaks into the surrounding connective tissue, resulting in a smooth surfaced painless nodule in the submucosal tissues. Mucous cysts of the sublingual and submandibular glands are referred to as ranulas. They present as either unilateral circumscribed lesions (subsequent to ductal obstruction and cystic dilatation) or plunging lesions (following extravasation of saliva herniating through the tissues of the floor of the mouth and the mylohyoid muscle) (Anastassov *et al*, 2000).

Salivary gland swellings are also caused by calculi (sialoliths, stones), which are calcifications of mucous plugs and cellular debris resulting from dehydration and glandular inactivity. They most frequently develop in the submandibular duct system. Sialoliths can occasionally be palpated using bidigital palpation techniques in the floor of the mouth (for submandibular and sublingual calculi) and parotid regions.

Salivary gland tumors are the subject of a future review in this series, and will only be briefly mentioned herein. Most salivary gland tumors are benign. The preponderance of benign salivary gland neoplasms occurs within the parotid gland, with the majority (80%) being pleomorphic adenomas. Malignant salivary gland tumor incidence increases with age, and these tumors are more common in the submandibular and sublingual glands. When epithelial neoplasms arise in the submandibular or sublingual glands, only 50% are benign (Martin, Salmaso and Onnis, 1989; Nagler and Laufer, 1997). Pleomorphic adenomas tend to be unilateral and most commonly present as an asympto-

matic mass in the tail of the parotid gland. They are slow growing, well delineated, and encapsulated.

Mucoepidermoid carcinoma is the most common malignant salivary gland tumor, followed by adenoid cystic carcinoma (cylindroma) (Lopes *et al*, 1999), acinic cell carcinoma, adenocarcinoma, squamous cell carcinoma, and carcinoma arising in a pleomorphic adenoma. The most frequently affected intraoral site is the palate followed by the upper lip. Signs and symptoms of a malignant salivary gland tumor include a swelling with facial nerve paralysis, pain, or facial paresis.

Systemic problems associated with salivary dysfunction

Several medical conditions are associated with salivary dysfunction (Table 3), the most common being SS, which will be discussed in considerable detail in a later issue in this series. SS is primarily a disease of women (it may be as prevalent as one out of every 2500 females) with a typical onset during the fourth or fifth decade of life (Thomas *et al*, 1998; Fox, Stern and Michelson, 2000; Pillemer *et al*, 2001). This is a debilitating systemic autoimmune disorder associated with inflammation of epithelial tissues, particularly exocrine glands (Tapinos *et al*, 1999), and is classified as primary SS or secondary SS. Primary SS involves salivary and lacrimal gland disorders with associated decreased production of saliva and tears. In secondary SS, the disorder occurs with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, and polyarteritis nodosa (Bloch *et al*, 1992).

Typical oral findings in the SS patient with xerostomia are as described above for other xerostomic patients. Swollen major salivary glands are common, because of salivary hypofunction, ductal inflammation, and acinar destruction. However, it is important to rule out malignancy in the presence of persistently and significantly enlarged salivary glands and neck lymph nodes. For example, there is a 44-fold increase in the frequency of B-cell lymphomas among SS patients (Kassan *et al*, 1978), and commonly these are non-Hodgkin's lymphomas of mucosa associated lymphoid tissues (MALT) (Royer *et al*, 1997; Voulgarelis *et al*, 1999). Diagnostic imaging (e.g. CT scans) and needle aspirates (for cytological and flow cytometric analyses)

Table 3 Systemic and exogenous sources of salivary dysfunction

Alzheimer's disease
Chemotherapy
Cystic fibrosis
Dehydration
Diabetes
Head and neck radiotherapy
HIV/AIDS
Lupus
Medications
Parkinson's disease
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Strokes

are helpful for establishing a diagnosis. If these investigations are equivocal, biopsy or removal of the swollen gland must be considered.

Other signs and symptoms of SS can be ascertained from a clinical examination. Impaired tear production results in inflammation and damage in the lacrimal glands. Systemic manifestations are frequent, including synovitis, neuropathy, vasculitis, and disorders of the skin, thyroid gland, urogenital system, respiratory, and gastrointestinal tracts.

The most commonly used diagnostic criteria are the 1996 revised European classification scheme (Vitali *et al*, 1996), which require at least four of six criteria to be met (Table 4). The key characteristics of SS are oral and ocular symptoms and signs of dryness, a positive labial salivary gland biopsy (focal, periductal, mononuclear cell infiltrates) and the presence of autoantibodies. Laboratory tests will frequently be positive for rheumatoid factor (90%), anti-Ro/SSA or anti-La/SSB (50–90%), with the presence of hypergammaglobulinemia (Bell *et al*, 1999). Antinuclear antibodies are present in ~80% of cases.

Other autoimmune conditions associated with SS have salivary dysfunction, including rheumatoid arthritis, scleroderma, and lupus (Arneberg *et al*, 1992; Russell and Reisine, 1998). HIV+ infected individuals and those with acquired immunodeficiency syndrome (AIDS) frequently experience salivary dysfunction from lymphocytic destruction of the glands and as a sequelae of medications (Shugars *et al*, 2000). Diabetes may cause changes in salivary secretions (Chavez *et al*, 2000, 2001), and associations have been made between poor glycemic control, peripheral neuropathies, and salivary dysfunction (Meurman *et al*, 1998). Alzheimer's disease, Parkinson's disease, strokes, and cystic fibrosis will inhibit salivary secretions. Dehydration, a common and under-diagnosed condition among the elderly, also has

been associated with salivary hypofunction (Ship and Fischer, 1997).

Medication-induced salivary dysfunction

The most common types of medications causing salivary dysfunction have anticholinergic effects (see future article in this series), via inhibition of acetylcholine binding to muscarinic receptors on the acinar cells (Baum *et al*, 1993). Any drug that inhibits neurotransmitter binding to acinar membrane receptors, or that perturb ion transport pathways, may also adversely affect the quality and quantity of salivary output. These medications include tricyclic antidepressants, sedatives and tranquilizers, antihistamines, antihypertensives (α and β blockers, diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors), cytotoxic agents, anti-Parkinsonian, and antiseizure/spasmodic drugs (Nederfors, Twetman and Dahlof, 1989; Nederfors *et al*, 1994, 1995; Streckfus *et al*, 1994; Hunter and Wilson, 1995; Loesche *et al*, 1995; Nederfors, 1996; Field *et al*, 1997; Pajukoski *et al*, 1997; Sreebny and Schwartz, 1997; Bergdahl and Bergdahl, 2000). Therefore, patients taking one or more drugs with antisialogogue sequelae should be followed carefully for developing signs and symptoms of salivary disorders.

Chemotherapy for cancer treatment has been associated with salivary disorders (Chaushu *et al*, 1995; Meurman *et al*, 1997a, 1997b; Harrison *et al*, 1998). These changes appear to occur during and immediately after treatment. Most patients experience return of salivary function to prechemotherapy levels, yet long-term changes have been reported (Meurman *et al*, 1997a, 1997b). Radioactive iodine (I-131) used in the treatment for cancers of the thyroid gland has also been reported to cause parotid but not submandibular dysfunction in a dose-dependent fashion (Allweiss *et al*, 1984).

Table 4 Sjögren's syndrome: revised European classification criteria^a

Ocular symptoms: a positive response to at least one of the following questions:

Have you had daily, persistent, troublesome dry eyes for more than 3 months?

Do you have a recurrent sensation of sand or gravel in the eyes?

Do you use tear substitutes more than three times a day?

Oral symptoms: a positive response to at least one of the following questions:

Have you had a daily feeling of dry mouth for more than 3 months?

Have you had recurrently or persistently swollen salivary glands as an adult?

Do you frequently drink liquids to aid in swallowing dry food?

Ocular signs: objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

Schirmer's I-test, performed without anesthesia (≤ 5 mm in 5 min)

Rose Bengal score or other ocular dye score (≥ 4 according to van Bijsterveld's scoring system)

Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1 , defined as a number of lymphocytic foci which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes per 4 mm^2 of glandular tissue (Daniels and Whitcher, 1994)

Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

Unstimulated whole salivary flow (≤ 1.5 ml in 15 min)

Parotid sialography showing the presence of diffuse sialectasis (punctate, cavitory or destructive pattern), without evidence of obstruction in the major (Rubin and Holt, 1957)

Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer (Schall *et al*, 1971)

Autoantibodies: presence in the serum of the following autoantibodies:

Antibodies to Ro/SSA or La/SSB antigens, or both

^aSee Vitali *et al* (1996)

Radiation-induced salivary dysfunction

Radiation therapy (RT) is a common component of treatment for head and neck cancers. Head and neck RT has serious and detrimental side-effects to the oral cavity including the loss of salivary gland function and a persistent complaint of a dry mouth (Valdez *et al*, 1993; Scully and Epstein, 1996; Henson *et al*, 1999). In addition, patients often experience the spectrum of oral-pharyngeal problems as a result of permanent salivary gland destruction (Parsons *et al*, 1994; Scully and Epstein, 1996). All cancer patients should be followed closely for developing salivary disorders and their adverse oral sequelae. The effects of RT on salivary gland function will be the subject of a subsequent article in this series.

Treatments for salivary gland disorders*Appropriate diagnosis*

As discussed earlier, treatment for salivary dysfunction begins with appropriate diagnosis. Once a diagnosis has been established, treatment is designed based upon the etiopathogenesis of the disorder and the prognosis. For example, if the etiology is medication-induced salivary dysfunction, then drug substitution or modification can ameliorate some symptoms of dry mouth (see below). If the prognosis for restoration of normal salivation is poor, such as with head and neck radiotherapy for oral cancers, then use of salivary replacements and stimulants may help.

Oral hygiene

Frequent dental evaluations are critical with a focus on preventing the myriad of oral disorders that develop

because of salivary hypofunction, and for instructing patients on proper oral hygiene (Atkinson and Wu, 1994; Fox, 1997). Patients, particularly older adults, must be reminded to maintain hydration (water is the drink of choice) to assist with xerostomia. Several habits, such as smoking, mouth breathing, and consumption of caffeine-containing beverages, have been shown to increase the risk of xerostomia. Limiting or stopping these practices should lessen the severity of dry mouth symptoms (Sciubba, 1994).

Salivary stimulation and salivary substitutes

Sugar-free chewing gum, candies, and mints can stimulate remaining salivary secretions (Table 5; Dawes and Macpherson, 1992; Jensen, Karatsaidis and Brodin, 1998; Davies, 2000), as well as enhance secretion of salivary sIgA (Proctor and Carpenter, 2001). In the absence of remaining salivary tissue, artificial saliva and lubricants may ameliorate some xerostomic symptoms. These products tend to diminish the sensation of oral dryness and improve oral functioning. Preference of products depends on effect duration, lubrication, taste, delivery system, and cost; many patients nevertheless primarily use water (Epstein and Stevenson-Moore, 1992). Several products available without a prescription include Biotene (mouthwash, toothpaste, and chewing gum), Optimoist (liquid spray saliva substitute), Saliva Orthana (mucin-based artificial saliva), Freedent (low-tack, sugar-free chewing gum), Xialine (xanthan gum-based saliva substitute), and Oralbalance gel (Davies *et al*, 1998; Regelink *et al*, 1998; Stewart *et al*, 1998; Davies, 2000; Rhodus and Bereuter, 2000; Warde *et al*, 2000; Jellema *et al*, 2001).

Table 5 Management of dry mouth-associated problems

<i>Xerostomia-associated problem</i>	<i>Management strategy</i>
Dental caries	Daily use of fluoridated dentifrice (0.05% sodium fluoride) Daily use of prescription fluoride gel (1.0% sodium fluoride, 0.4% stannous fluoride) Application of 0.5% sodium fluoride varnish to teeth Dental examinations at least every 6 months and intraoral radiographs for early diagnosis at every 12 months
Dry mouth	Sugarless gums, mints, lozenges Artificial salivary replacements Prescription sialogogues: pilocarpine 5 mg tid and qds; cevimeline 30 mg tid Lubricants on lips q2h
Dysgeusia Dysphagia	Use of fluids during eating Careful eating with fluids Copious use of fluids during meals
Oral candidiasis	Avoid dry, hard, sticky and difficult to masticate foods Antifungal rinses: Nystatin oral suspension 100 000 units mL ⁻¹ , rinse qid Antifungal ointments: Nystatin ointment applied qid Antifungal lozenges dissolved in mouth qid: Nystatin pastilles 200 000 units; Clotrimazole troches 10 mg; Nystatin vaginal suppositories Denture antifungal treatment: daily hygiene, soak prosthesis for 30 min in benzoic acid, 0.12% chlorhexidine, or 1% sodium hypochlorite
Bacterial infections	Systemic antibiotics × 10 days: Amoxicillin with clavulanate 500 mg q8h; Clindamycin 300 mg tid; Cephalexin 500 mg q6h Increase hydration
Poorly fitting prostheses	Salivary stimulation with sugarless gums, mints, lozenges Soft and hard-tissue relines by dentist Denture adhesives

Treatment with cholinergic agonists

Treating xerostomia with medications that enhance salivation is another therapeutic option (Table 5; Atkinson and Baum, 2001), particularly in the relatively healthy person for whom polypharmacy may not be a critical concern. Secretagogues such as pilocarpine can increase secretions and diminish xerostomic complaints in patients with sufficiently remaining exocrine tissue (e.g. Johnson *et al*, 1993; Niedermeier *et al*, 1998; Vivino *et al*, 1999). Pilocarpine is typically given in a dosage of 5 mg orally three times a day and before bedtime. When taken ~30 min before mealtime, patients may benefit from the increased salivation in eating their meal. The total daily dose should not exceed 30 mg. Adverse effects include increased perspiration, greater bowel and bladder motility, and feeling hot and flushed. Patients with a history of bronchospasm, severe chronic obstructive pulmonary disease, congestive heart disease, and angle closure glaucoma should not take pilocarpine.

A new secretagogue, cevimeline, has recently been approved by the United States Food and Drug Administration for the treatment of dry mouth in SS in a dosage of 30 mg orally three times daily (Cevimeline, 2000). Like pilocarpine, it is a muscarinic agonist that increases production of saliva. Pilocarpine is a non-selective muscarinic agonist, whereas cevimeline reportedly has a higher affinity for M1 and M3 muscarinic receptor subtypes. As M2 and M4 receptors are located on cardiac and lung tissues, cevimeline can enhance salivary secretions while minimizing adverse effects on pulmonary and cardiac function. Patients with uncontrolled asthma, significant cardiac disease and angle closure glaucoma should not take cevimeline.

Bethanechol, another cholinergic agonist, has been used (25 mg tid) to stimulate saliva in post head and neck radiotherapy patients, with few reported significant side-effects (Epstein *et al*, 1994).

Acupuncture

Over the last decade there has been some interest in using acupuncture techniques to enhance salivation (Blom *et al*, 1996; Andersen and Machin, 1997; Blom and Lundeberg, 2000). There are data suggesting that acupuncture therapy can maintain an improvement in stimulated saliva up to 6 months after the completion of radiotherapy (Blom and Lundeberg, 2000). Although this treatment modality is not commonly utilized, it presents a treatment option for patients who respond well to muscarinic agonists (e.g. pilocarpine, cevimeline) yet have difficulty taking these medications because of secondary side-effects.

Treatment of salivary dysfunction-associated dental caries

Daily topical fluoride use and antimicrobial mouth rinses help prevent caries in patients with reduced salivary flow (Table 5; Meyerowitz *et al*, 1991; Sweeney *et al*, 1997; Fox, 1998; Rhodus and Bereuter, 2000). Strategies are directed towards prevention and early detection of various lesions, remineralization of incipi-

ent lesions, and permanent restoration of new and recurrent decay. Non-prescription mouth rinses (0.05% sodium fluoride) can be used twice daily to prevent demineralization and induce remineralization (Meyerowitz *et al*, 1991). Stronger prescription fluoride formulations (1.0 or 1.1% sodium fluoride, 0.4% stannous fluoride) are applied daily by tooth brushing or in custom-made soft acrylic trays. In-office fluoride applications (gel or foam formulations), varnishes, and pit and fissure sealants can prevent rapid decay of tooth structure in patients with severe salivary hypofunction.

Treatment of salivary dysfunction-associated oral infections

The secondary effects of salivary hypofunction on soft tissues also require appropriate diagnosis and treatment. Desiccated oral mucosal tissues are more susceptible to ulcerations and traumatic lesions. Soft tissue management includes maintaining mucosal integrity to avoid local (Chaushu *et al*, 2000) or systemic infections from oral microflora. Dry mouth-induced oral lesions are susceptible to developing secondary infections by microbial flora that normally inhabit the oral cavity as well as by exogenous organisms (Pizzo *et al*, 1993; Rolston and Bodey, 1993). Initial therapy for salivary infections (e.g. parotitis) includes systemic antibiotics (amoxicillin with clavulanate, clindamycin, or cephalexin), hydration, and salivary stimulation. Viral infections of salivary glands usually resolve after symptomatic treatment, but in the severely medically compromised patient, systemic antiviral therapy (acyclovir, valacyclovir, ganciclovir, foscarnet) should be initiated. Concomitant use of antimicrobial mouth rinses (e.g. chlorhexidine 0.12%) may also be helpful.

Oral candidiasis is the most frequent oral infection secondary to dry mouth, and is treated initially with topical antifungal agents (Shay, Truhlar and Renner, 1997; Epstein and Polsky, 1998). Oral rinses, ointments, pastilles, and troches are effective for most forms of oral candidiasis (Table 5), and systemic antifungal therapy (e.g. Ketoconazole, Fluconazole) should be reserved for refractory disease and immunocompromised patients. Dentures may harbor fungal infections and thus require treatment. Patients must be instructed to perform daily hygiene of the appliance, and to keep the prosthesis out of the mouth for extended periods and while sleeping. Prostheses can be soaked for 30 min in solutions containing benzoic acid, 0.12% chlorhexidine, or 1% sodium hypochlorite and then thoroughly rinsed. A few drops of Nystatin oral suspension or a thin film of Nystatin ointment can be applied to the inner surface of a denture after each meal. Angular cheilitis should be treated with a combination of antifungal and anti-inflammatory agents (Nystatin-triamcinolone acetonide ointment; apply qid). It is important to note that Nystatin and Clotrimazole troches contain sugar, and therefore the patient with severe salivary gland dysfunction at risk for dental caries should use vaginal Nystatin tablets.

Treatment of salivary dysfunction-associated denture problems

Retention of removable prostheses can become impaired and painful in the presence of desiccated oral mucosa tissues and the lack of adequate salivary output. Daily oral hygiene of dentures and prosthesis-bearing mucosal tissues is important, as is regular observation for Candidal infections. Careful chewing and swallowing is advised with the addition of frequent sips of liquids to avoid choking and aspiration. Denture problems can be diminished with frequent dental examinations to identify sore spots and to enhance adhesion with soft- and hard-tissue relines (Zwetchkenbaum and Shay, 1997).

Management of salivary dysfunction-associated digestive problems

Dry mouth-associated eating and swallowing problems can inhibit intake of fiber-rich foods, restricting some adults to a primarily soft and carbohydrate diet. Accordingly, patients must be counseled on a well-balanced nutritionally adequate diet and the importance of limiting sugar intake, particularly between meals. Problems with swallowing may be treated with oral moisturizers and lubricants and careful use of fluids during eating. At night, bedside humidifiers can provide some assistance for patients experiencing significant nocturnal oral dryness.

Treatment of Sjögren's syndrome

Sjögren's syndrome requires management of xerostomia, keratoconjunctivitis (Pflugfelder, 1998), and its autoimmune and inflammatory manifestations (Fox *et al*, 1993, 1996; Kruize *et al*, 1993; Skopouli *et al*, 1996; Price *et al*, 1998). Immunomodulatory therapy (Oxholm, Prause and Schiodt, 1998; Pflugfelder, 1998; Fox, 2000), replacement of destroyed salivary gland tissue by artificial salivary glands (Baum *et al*, 1999; Aframian *et al*, 2000), and the possibilities for gene therapy (Baum *et al*, 2000; Yamano and Baum, 2000) are under active investigation. Currently, effective therapy requires a multidisciplinary approach including ophthalmologists, dentists, rheumatologists, and other specialists as necessary. Repeated monitoring is required to diminish the number and severity of exacerbations, which is critical to delay the onset of permanent exocrine and organ dysfunction.

Masticatory (sugarless gums), gustatory (sugarless mints and lozenges) and pharmacologic (Pilocarpine, Cevimeline) stimulants are effective for patients with SS who have remaining salivary gland tissue. These therapies are also effective for patients who have other systemic diseases associated with salivary dysfunction (e.g. HIV, diabetes, Alzheimer's disease). Prescription of cholinergic agonists must be conducted in collaboration with primary medical providers, to avoid polypharmacy complications. In the late-stage Sjögren's patient, where all fluid producing acinar cells have been replaced by connective tissue, salivary stimulants will not be helpful. These patients require fluid replacements with artificial saliva, water and sugarless beverages.

Management of medication-induced salivary dysfunction

Treatment of medication-associated salivary dysfunction requires consultation with the patient's physicians. The first step is to decrease the number of medications a person is taking that cause salivary hypofunction (Sreebny and Schwartz, 1997). When the administration of xerostomia-associated drugs is inevitable, substitution with similar acting medications with fewer xerostomic side-effects is preferred. Some classes of medications provide better opportunities for substitution. For example, if a patient is taking an antihypertensive, a diuretic could be changed to an angiotensin converting enzyme inhibitor. Serotonin specific reuptake inhibitors have been reported to cause less dry mouth than tricyclic antidepressants (Hunter and Wilson, 1995; Trindade *et al*, 1998). Milnacipran is a new antidepressive drug and a combined norepinephrine/serotonin reuptake inhibitor, and was demonstrated to provide improved outcomes with less dry mouth symptoms compared with clomipramine in a double-blind, randomized, parallel-group study for treatment of major depression (Leinonen *et al*, 1997). A new acetylcholinesterase inhibitor (Donepezil) marketed for treatment of memory loss and behavioral deterioration associated with Alzheimer's disease is associated with few complaints of dry mouth (Jacobsen and Comas-Diaz, 1999). For treatment-resistant schizophrenia, olanzapine (an antipsychotic drug and a structural congener of clozapine) demonstrated similar efficacy to chlorpromazine, yet had 50% fewer side-effects of dry mouth (Conley *et al*, 1998).

Another study demonstrated that a controlled-release formulation of oxybutynin chloride (antispasmodic agent; Ditropan XL) given once daily maintained relatively constant plasma drug and metabolite concentrations, produced fewer dry mouth complaints and greater salivary flow rates compared with immediate-release oxybutynin given twice daily (Sathyan, Chancellor and Gupta, 2001). Further, saliva output was maintained at predose levels throughout the day with extended-release oxybutynin, compared with lower salivary output in subjects taking immediate-release oxybutynin twice daily and those taking tolterodine tartrate (another anticholinergic agent used to suppress involuntary bladder contractions in urinary incontinence) (Chancellor *et al*, 2001). Clearly, there are some drug substitutions that will provide disease-treating efficacy with fewer xerostomic side-effects.

Salivary output is lowest during night-time, and anticholinergic drugs taken before bedtime will produce a greater inhibition during these hours. If these medications can be taken during the daytime, patients can manage better the xerostomic effects and avoid waking at night because of severe xerostomia. Another strategy, if applicable, is to divide drug administration into several dosages, which will minimize unwanted side-effects from a large single dose. In summary, consideration of the xerostomia-causing profile, dosage and timing of administration of medications can assist in diminishing the unwanted xerostomic side-effects of many prescription and non-prescription pharmaceuticals.

Treatment of radiotherapy-induced salivary dysfunction
Head and neck radiotherapy causes significant and permanent salivary hypofunction and xerostomia, and therefore requires a lifetime of supportive care (Parsons *et al*, 1994; Scully and Epstein, 1996; Epstein and Chow, 1999). Techniques described above for other xerostomia-associated problems should be implemented in patients who have received head and neck radiotherapy.

Importantly, strategies are available to assist in diminishing the salivary dysfunction that develops during radiotherapy. Using salivary-sparing radiotherapy techniques, significant dose reductions have been achieved to parotid glands on the contralateral side of the primary tumor, resulting in continued salivary output, a reduction of xerostomia, and improvement of xerostomia-related quality of life (Eisbruch *et al*, 1996, 1998, 1999; Henson *et al*, 1999, 2001). Further, it appears that reducing the dose to the salivary glands does not impair radiation efficacy with respect to tumors and lymph nodes considered to be at risk for cancer spread, and that long-term survival may not be reduced with these radiation-sparing techniques (Dawson *et al*, 2000; Eisbruch *et al*, 2001a, 2001b).

Another technique available during radiotherapy is the concomitant use of several medications that may increase salivation and provide cytoprotection. Amifostine (a broad-spectrum cyto- and radio-protectant) may provide cytoprotection against myelotoxicity, nephrotoxicity, mucositis, and xerostomia associated with various chemotherapy and radiation modalities (Buntzel *et al*, 1998a, 1998b; Capizzi and Oster, 2000). Pilocarpine can improve symptoms of xerostomia when given during (Jacobs, 1996; Zimmerman *et al*, 1997) and after the completion of radiotherapy (Johnson *et al*, 1993; LeVeque *et al*, 1993; Davies and Singer, 1994; Rieke *et al*, 1995; Hamlar *et al*, 1996). Bethanechol, a non-specific muscarinic agonist (Epstein *et al*, 1994), and Cevimeline, a more specific muscarinic agonist (Cevimeline, 2000) may be useful for patients with remaining salivary tissue.

Treatment of salivary gland lesions and tumors

This subject will be covered in greater detail in a future article in this series. For 'completeness', a brief description is provided here. Treatment starts with an appropriate diagnosis including histopathological evaluation and imaging techniques (see above). Mucocoeles and ranulas, the most common salivary lesions, require surgical excision and possible marsupialization of the cyst. Recurrence of mucocoeles is common, because of the frequency of lacerating an adjacent minor salivary gland during surgery.

Treatment and prognosis for salivary gland tumors varies significantly and is dependent upon size and grade of the neoplasm as well as the histologic classification (Million and Cassisi, 1994). Benign tumors (pleomorphic adenoma, monomorphic adenoma) require careful excision as they are encapsulated and residual tissue after surgery can increase the risk of tumor recurrence. For example, 1.6% of pleomorphic adenomas recur following surgical excision (Phillips and Olsen, 1995).

Recurrent lesions are frequently multinodular, and treatment is determined by the extent of the disease, prior therapy, and amount of recurrence. Malignant degeneration is uncommon (carcinoma arising in a pleomorphic adenoma) and most often arises in tumors that have been present for at least 25 years, or tumors that have had multiple recurrences and numerous failed therapies (Gnepp, 1993; Phillips and Olsen, 1995).

Recurrent salivary gland tumors require more extensive treatment, including wider surgical margins and postsurgical radiotherapy. Malignant salivary tumors are excised including regional lymph nodes at risk for tumor spread. A full course of external beam (typically 60 Gy) radiotherapy is used as an adjuvant 3–4 weeks after surgery (Parsons *et al*, 1994). Chemotherapy has been utilized for salivary gland cancers only more recently, and has not been shown to definitively increase the odds of cancer survival. Presently, chemotherapy is indicated only for pain relief in symptomatic patients who have either recurrent cancers or non-resectable tumors (Kaplan, Johns and Cantrell, 1986; Spiro, 1997).

Preventing salivary dysfunction

Prevention of salivary gland disorders starts with regular examinations for all patients. This should include: (1) palpation of all major salivary glands; (2) assessment of clear salivary output from Wharton's and Stenson's ducts; (3) examination for the signs and symptoms associated with a dry mouth; and (4) current review of the patient's medical history and medications. Importantly, those individuals at risk for developing salivary dysfunction (e.g. those taking multiple medications) must be followed thoroughly. Querying patients about xerostomia should also be a component of every clinical examination (Table 1). However, in the presence of salivary hypofunction, older persons are less likely to complain of xerostomia, and therefore may be at increased risk of developing its sequelae (Fischer and Ship, 1997; Ship and Fischer, 1997; Patel *et al*, 2001). Good communication between all clinicians is critical for limiting salivary dysfunction in at-risk patients.

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