

# *Oral Health in Cancer Therapy*

## *A Guide for Health Care Professionals*

Third Edition



The first edition of Oral Health in Cancer Therapy: A Guide for Health Care Professionals emerged from a February 1999 consensus conference convened by the Dental Oncology Education Program cosponsored by the Texas Cancer Council and the Oral Health Education Foundation. In February 2008 a similar consensus conference was convened for the purpose of updating the content of the second edition of the Oral Health and Cancer Therapy monograph. There is an acknowledged lack of evidence-based research in the prevention and management of the oral complications of cancer therapy. The information contained in this edition of the monograph reflects the best evidence-based and empirical knowledge of the nationally recognized experts in the field who participated in the conference. No individual section of this edition is attributed to a single author as the content represents a truly generous, collaborative effort on the part of all the authors.

The personal and financial commitment of the following individuals and organizations was pivotal to the conference's success:

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## CONFERENCE AGENDA February 21 - 22, 2008

*Oral Mucositis*

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*Bisphosphonate-Induced Osteonecrosis*

**Michael Huber, DDS**

*Chemotherapy-Related Infections*

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# ORAL HEALTH IN CANCER THERAPY

A GUIDE FOR HEALTH CARE PROFESSIONALS

Third Edition

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We are indebted to the speakers, authors and conference participants without whom the third edition would not have been possible. No individual section of this edition is attributed to a single author as the content represents a truly generous, collaborative effort on the part of all the authors.

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## BACKGROUND

At the time of a cancer diagnosis, the patient and family are overwhelmed with information, treatment options and decisions that must be made with all due speed. Coupled with the emotional impact of a cancer diagnosis, these factors converge to create one of the most difficult physical and emotional periods of life. Coordination by a comprehensive oncology “team” can significantly reduce the emotional toll and contribute to successful treatment outcomes. Pre-treatment oral assessment and supportive oral care during and after cancer therapy can increase quality of life and decrease higher treatment and supportive care costs.

Cancer treatment is no longer exclusively delivered in large cancer centers staffed by a multidisciplinary team. Furthermore, therapeutic modalities are no longer considered in isolation, nor are the oral complications. Clinicians across the spectrum of healthcare in the community must by necessity become the patient’s treatment team. Compromised oral health prior to, during and following cancer therapy dramatically affects treatment outcomes and quality of life. The intent of this monograph is to provide the most current, practical clinical information and guidance to the practitioner to assist in providing patients and their families with appropriate services and advice prior to, during and following cancer therapy. The clinical orientation is evidenced by the organization of sections by treatment modality and the stage of cancer therapy (pre-therapy, during therapy and post-therapy).

### INTENT OF THE MONOGRAPH

The intent of this monograph is to provide current, practical clinical information and guidance to the practitioner outside the major cancer treatment center to assist in providing their patient family with appropriate advice as they progress through therapy at a distant site or the information to provide a continuum of oral health care in preparation for cancer therapy, during therapy and after therapy.

### ORGANIZATION OF THE MONOGRAPH

Treatment modalities are addressed in individual sections, while the concept of care appropriate to the stage of cancer treatment is preserved within sections. Because many of the oral complications manifest across treatment modalities, specifically management of hyposalivation and pain, these are addressed in detail in individual sections and referenced as appropriate within the treatment modality sections.

A number of factors, including but not limited to growth and development, preclude addressing cancer therapy and oral health in children in the context of this monograph. The most recent position paper issued by the American Academy of Pediatric Dentistry is reprinted here with the permission of the Academy.

### DEDICATION

This monograph is dedicated to all the men and women working in the field of oncology who have committed themselves to the tireless tasks, frustrations and rewards of helping individuals meet the challenges of cancer.

## HEAD AND NECK RADIATION

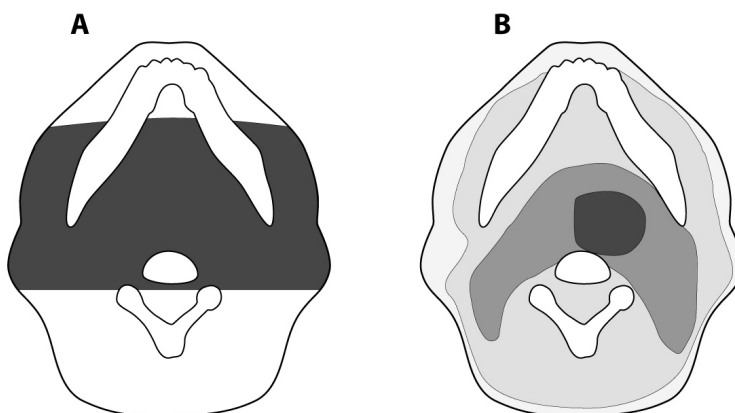
### INTRODUCTION

Radiation therapy is routinely used for tumors of the head and neck. It may be used in the primary setting as the sole treatment or after surgery as adjuvant therapy. It may be given by itself or with chemotherapy. Recently, immunotherapy has emerged as an adjunct to radiation therapy. Cetuximab, or epidermal growth factor inhibitor, has been shown to improve cure rates for oral cancer when given with radiation therapy.

Generally radiation therapy is given once a day five days per week. The radiation schedule is termed "fractionation" and standard fractionation refers to treatment once a day Monday through Friday. Other schedules have been used to intensify treatment for more advanced tumors and this is called accelerated fractionation or in some instances hyperfractionation. Oral complications are related to the site radiated, the total radiation dose, the fractionation schedule and integration with other cancer therapies such as chemotherapy. Most tumors of the head and neck region are squamous cell carcinoma, which require relatively high doses of radiation for local tumor control. Typically 50 Gray (Gy) of radiation, which corresponds to a five week course, is needed for microscopic disease control and 70 Gy is needed for gross tumor control. Chemotherapy must also be used to control locally advanced tumors. Most radiation for head and neck tumors is given externally, where the patient lies on a table and the machine spins on an axis to deposit radiation from different directions.

Prior to approximately 1995, radiation was often given using opposed lateral portals, meaning that all the tissue between the portals received the same dose. In figure 1a this is represented as a constant shade of gray throughout the exposed area. Over the last 10-15 years, most centers have adopted what is called intensity modulated radiation therapy (IMRT). With this method, the radiation beam is not static and the blocks in its way are constantly moving so radiation can be deposited in a specific pattern. Planning for IMRT involves a team of physicians, physicists and dosimetrists. An IMRT treatment plan for oropharyngeal carcinoma is shown in Figure 1b where higher radiation doses are represented by the darker shading and lower doses are represented by progressively lighter shading. As illustrated, the high dose or "hot spot", represented by the darkest shading, can be localized in the tumor and surrounding tissues are preferentially spared. In this case the darkest tumor area would receive approximately 70 Gy and the lightest area of the anterior mandible would receive only 25 Gy. Perhaps the greatest contribution of IMRT is sparing of the parotid glands. Numerous authors have shown that if the mean dose to the parotid can be limited to 24-26 Gy, reasonable salivary flow can be maintained. Of course, there is still some collateral irradiation to other tissues and while high doses to normal oral mucosa or mandible, for example, can be avoided, low doses to a larger volume often occur, and the clinical significance of this is still uncertain. This dose gradient, however, is critical when performing dental evaluations on patients who have received IMRT, since the dose to certain regions of the mandible will differ, as is evident in Figure 1b. The radiation oncologist should furnish dental specialists with the actual isodose plan so that they can determine exactly what dose was received when making post-radiation management decisions. Unfortunately, this information is not available to the dentist before radiation is given, so it cannot be used for pre-radiation decisions.

*Figure 1: Axial view of radiation therapy for an oropharyngeal squamous cell carcinoma.*



1A: A fixed beam of conventional radiation therapy applied laterally delivers a consistent, high dose to all of the area within the dark shading. Unshaded areas receive no radiation exposure.

1B: A constantly moving beam with IMRT varies the radiation dose depending on the location. The darkest area represents the tumor location and receives the highest dose of radiation. Lighter shades of gray depict progressively lower doses of radiation as the exposure gets further and further from the tumor reaching the lowest dose at the periphery. In contrast to conventional radiation therapy, all areas receive some radiation exposure. (Bony structures include the mandible and the spinal column.)

## HEAD AND NECK RADIATION THERAPY

Other forms of radiation therapy are available to treat head and neck cancers. Brachytherapy involves inserting radioactive wires directly into a tumor, such as in the lip. This delivers a concentrated radiation dose to the tumor, but also delivers a large dose to the immediately surrounding tissue. Therefore, these patients may be at increased risk for complications such as osteoradionecrosis in areas of the mandible adjacent to the tumor.

### SIDE EFFECTS OF HEAD AND NECK RADIATION

Radiation side effects occur in two categories with respect to time. Acute effects are those occurring during treatment or shortly afterwards. Late effects may occur months or even years after therapy.

#### ***Mucositis***

Mucositis is an acute effect with a complicated pathogenesis resulting in early cell death in the epithelial basement membrane. Clinically, mucositis typically begins in the second week of radiation therapy and subsides slowly several weeks after radiation therapy is complete. Mucosa in the radiation field often becomes atrophic and prone to ulceration. Patients with mucositis are at increased risk of infection and should exercise good oral hygiene.

#### ***Hypogeusia/Dysgeusia***

Permanent taste loss may occur at a dose of 60 Gy if the tongue is largely within the high dose volume. Below this level, recovery usually takes several months. Both mucositis and decreased saliva flow may contribute to taste alteration. Chemoreceptors on the dorsal tongue that allow discriminative taste acuity can be markedly affected by mucosal ulceration that can last months to years.

#### ***Xerostomia***

Radiation of salivary glands results in atrophy of the secretory cells and subsequent dry mouth or xerostomia. The degree of xerostomia is related to the radiation dose and amount of salivary glandular tissue in the radiation volume. Although IMRT has reduced the severity of xerostomia, it still occurs to a variable degree in most patients. As mentioned previously, doses as low as 25 Gy can result in hypofunction. Serous glands degenerate faster than mucous glands, resulting in saliva that is more acidic and thick and does not flow readily. If the normal functions of saliva are compromised, a host of abnormalities can occur, including decreased remineralization capacity, impaired antimicrobial capacity and mouth cleansing, taste alterations, and difficulties in oral function such as deglutition, mastication and speech.

#### ***Osteoradionecrosis (ORN)***

Osteoradionecrosis is a complex process chiefly related to small blood vessel changes that result in an impaired capacity for the bone to heal. ORN is a late side effect (typically occurs at least one year after treatment) and the risk of ORN increases over time. ORN is confined primarily to the mandible, as ORN of the maxilla is rare. Although it can occur after lower doses, ORN is most commonly associated with radiation doses of >60 Gy. Pretreatment dental management should strive to eliminate or reduce the possibility of subsequent foci for ORN. As mentioned above, patients who receive brachytherapy may be at particular risk for ORN.

#### ***Dental Caries***

Radiation-induced atrophy of salivary gland tissue leads to a decrease in quality and quantity of saliva, reducing the patient's normal antimicrobial and remineralizing capacity, which creates a higher risk for infection. In the absence of daily fluoride treatment and proper oral hygiene maintenance, there can be rapid destruction of the dentition.

#### ***Trismus***

Contraction of the masticatory muscles and TMJ capsule, usually occurring 3-6 months after radiation therapy, occurs with unpredictable frequency and severity. It is accentuated by some surgical resections and higher radiation dosing to the pterygoid regions. This problem tends to be more apparent in treatment of nasopharyngeal and oropharyngeal carcinoma, particularly when opposed lateral portals were used.

#### ***Loss of periodontal attachment***

Increased tooth loss and greater periodontal attachment loss over time is seen in teeth included in high-dose radiation fields.

#### ***Nutritional Deficiency***

Nutritional deficiencies occur secondarily as a result of mucositis, xerostomia, hypogeusia and loss of appetite that can make eating a painful chore. Symptoms include rapid weight loss, dehydration, stomatitis, or secondary oral infections such as candidiasis.

## ORAL MANAGEMENT

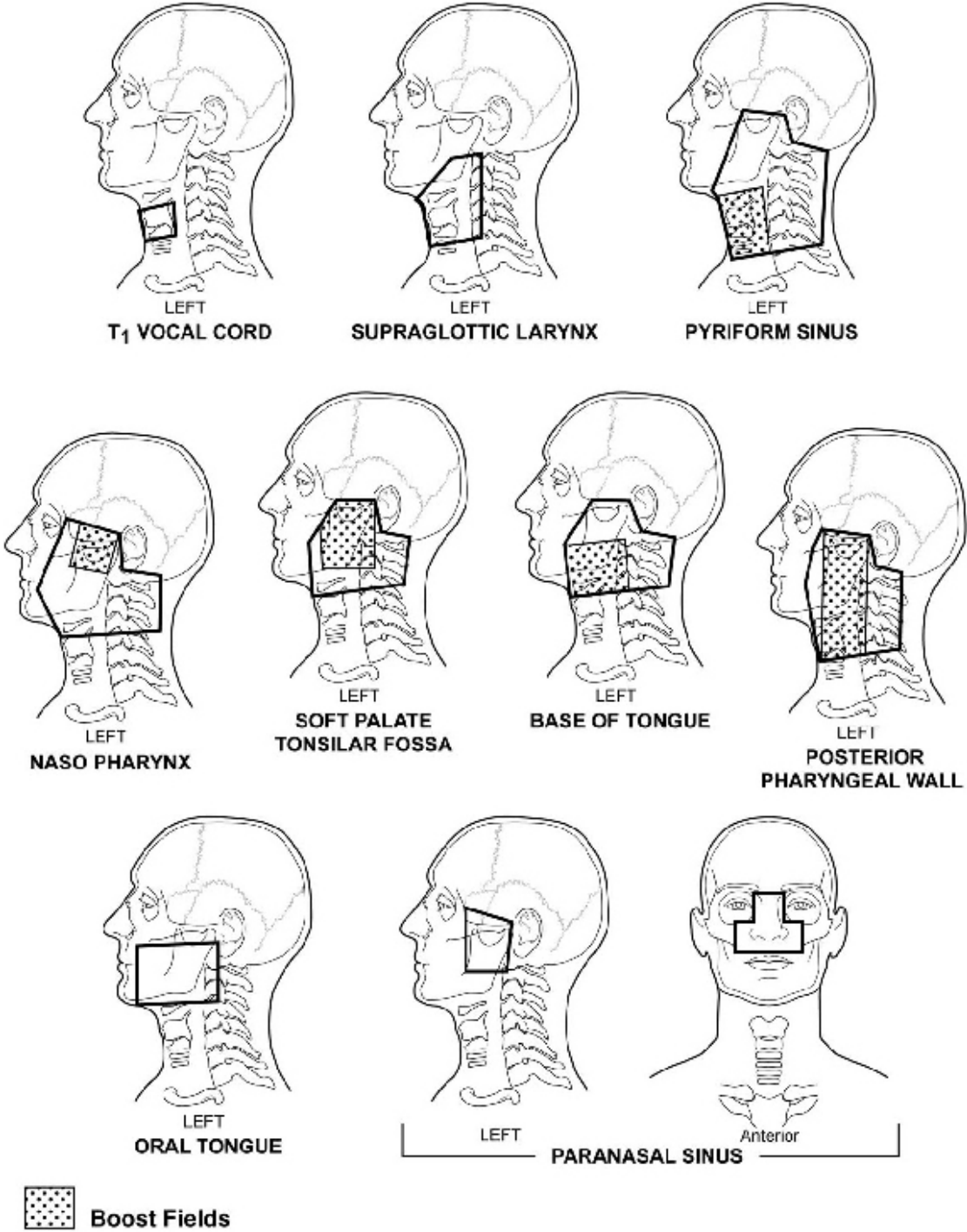
### *Before and During Radiation*

Before radiotherapy, the dentist must obtain appropriate radiographs to establish baseline dental evaluation and identify pulpal, periapical and/or periodontal pathology that require immediate attention. Complete periodontal charting should be done to establish baseline dental evaluation and identify subsequent periodontal problems. It is crucial to eliminate sources of intra-oral trauma and infection such as calculus, sharp teeth, ill-fitting prostheses/appliances, or anything that could cause intra-oral trauma. Impressions of teeth should be taken to fabricate custom trays for fluoride delivery. Teeth that are non-restorable, those with moderate to severe periodontal disease and partially erupted mandibular third molars should be extracted if they are within the radiation field. The patient's ability to maintain meticulous oral hygiene for the rest of their life must also be assessed and should influence the decision to extract other, relatively sound teeth within the radiation field. If patients have previously exhibited poor dentition, it is predictable that this will continue and put these patients at risk for osteoradionecrosis.

The dentist must consult closely with the radiation oncologist to determine the timing and extent of dental treatment needed prior to radiation therapy. As with chemotherapy, dental treatment should be avoided while the patient is receiving radiation. At least 14 days should be available for healing of any dental surgery before radiation therapy begins. The dentist must know the area of the jaws that will receive radiation exposure and the doses to be delivered. With conventional radiation, the areas of exposure are termed the radiation ports. In general, radiation ports are determined based on the location of the tumor. Figure 2 shows the ports commonly used for a given tumor location. The large outline designates the extent of radiation exposure. The smaller dotted areas show where boosted doses may be delivered. For example, radiation for a base of tongue cancer would tend to spare the anterior mandible but not the posterior mandible. Therefore the posterior mandible in this patient would be at greatest risk of ORN. This figure is used as a guide. With each case it is critical to obtain the exact area of radiation exposure for that patient. As mentioned previously, most centers now utilize IMRT for treatment of head and neck tumors. The patient receives their radiation based on the isodose plan. However this is not finalized until just before the patient begins radiation treatment after they have received any needed oral care. Therefore, the dentist will not have the isodose plan available to make pre-radiation decisions. It is not currently known if IMRT will affect oral tissues differently than conventional radiation therapy. The exception to this is sparing of the parotid glands discussed previously. It is recommended that until the effects of IMRT are better understood, estimated radiation doses to oral structures should still be based on the tumor location using Figure 2 as a guide.

In some cases the tumor size and growth rate may require that radiation therapy be initiated immediately and not allow for 14 days of healing after dental surgery. In this case the dental surgery should not be done during radiation therapy, but performed as soon as radiation therapy has ended and the patient has recovered from this treatment, probably within four to six weeks. This should not be delayed, since bone changes associated with radiation therapy may worsen over time.

*Figure 2: Radiation fields for the most common head and tumor locations.*



The field is within the solid black line. The dotted area signifies where higher doses of radiation or boosts may be given for that particular tumor. Note the areas of the mandible and maxilla that are included in the field. These illustrations are given to show typical fields. Such fields should be confirmed by the patient’s radiation oncologist. (Used by permission of Dr. Todd Williams.)

**Oral Hygiene**

The importance of oral hygiene in these patients cannot be overemphasized. If patients are committed to lifelong meticulous oral hygiene and topical fluoride therapy, they need not lose their teeth as a result of radiation therapy. However as mentioned previously, this is the rare patient. Patients with head and neck cancer typically have risk factors (chronic tobacco and alcohol use) that are not associated with good compliance. Therefore, it is important for the dentist to assess the potential for oral hygiene compliance before radiation therapy.

**Fluoride Therapy**

Xerostomia associated with therapeutic radiation to the head and neck is usually permanent. It is imperative to communicate the importance of life-long fluoride therapy to the patient and family. Ideally, the patient should be started on fluoride therapy prior to radiation treatment. This may take the form of fluoride gel carriers, brush-on gel, or fluoride rinses. Fluoride therapy education should be repeated and reinforced following therapy. (See Xerostomia Management at the end of this chapter.)

**Denture Care**

Removable appliances should not be worn during treatment, if possible, and dentures should be removed at night. Clean the prosthesis daily with a denture brush and toothpaste and soak in commercial cleanser or water. If a patient shows any evidence of denture stomatitis this should be treated as a *Candida* infection.

**Endodontics**

Root canal therapy can be done as a single procedure for carious teeth with pulpal involvement confined to the tooth. Teeth outside the radiation field with necrotic or infected periapical tissue may have root canal therapy. For teeth with apical disease within the radiation field, extraction is preferred. All teeth with periapical radiolucencies that have been previously treated endodontically should be assessed for clinical signs and symptoms of current infection.

**Oral and Maxillofacial Surgery**

Extraction should be considered for partially erupted third molars, teeth with pericoronitis, non-restorable fractured teeth, teeth with unresolved periapical lesions, teeth that lie within the radiation field in patients where long-term oral hygiene compliance is questionable and teeth with advanced periodontal disease. Extractions should be performed with minimal trauma. Particular attention should be directed toward tori in the radiation field. Mandibular tori should be removed with mandibular extractions to facilitate the future construction of prostheses. Sufficient healing should be allowed prior to initiation of therapy. While 14-21 days is optimal, it may not be possible due to concern for disease progression.

**Orthodontics**

Orthodontic bands and appliances that may cause trauma to oral mucosa should be removed. If bands are not removed, soft wax/plastic mouthguards may be used to cover them during periods of oral inflammation or ulceration.

**Periodontics**

Pretreatment prophylaxis and/or scaling are recommended for all patients. Teeth with 5 mm or greater periodontal pocketing should be evaluated for extraction if they are in the field of radiation, and teeth that display advanced bone loss, excessive mobility, purulence or excessive bleeding on probing should be extracted.

**Xerostomia Prevention**

On the basis of data from a Phase III randomized trial in patients with head and neck cancer, some institutions use amifostine, a radioprotector, during radiation therapy. Amifostine was found to significantly reduce the overall incidence of acute xerostomia, from 78% to 51%. Moreover, the dose of radiation required to cause this side effect in 50% of all patients was markedly higher in those patients receiving amifostine compared with those who did not (60 Gy v 42 Gy, respectively;  $p < .0001$ ). One year after the completion of treatment, chronic xerostomia was significantly less frequent in patients who received amifostine (34% v 57%, respectively;  $p = .002$ ). Also, 1 year after radiotherapy completion, 72% of the patients who received amifostine could produce more than 0.1 ml of saliva, a clinically relevant volume, compared with only 49% of the patients who did not. Despite these results, many head and neck radiation oncologists do not routinely use this agent, likely due to the problems associated with administration which include hypotension, allergic reactions and nausea.

## HEAD AND NECK RADIATION THERAPY

### **Mucositis**

Mucositis is marked by inflammation and ulceration of the mucosal lining of the mouth, pharynx, esophagus and GI tract due to the direct cytotoxic effects on the epithelial cells. Tissues demonstrate thinning of the mucosa, submucosal ulceration and necrosis. The buccal mucosa, tongue, lip mucosa, floor of mouth, and soft palate are the most frequently affected intraoral sites. Lesions are often very painful and can significantly affect a patient's quality of life. Mucositis may be exacerbated by secondary infection with bacteria, fungi and viruses. In severe cases, mucositis may prevent oral intake of both liquids and solids due to severe pain. Intraoral surfaces demonstrating mucositis may also serve as a portal of entry for organisms to the systemic circulation.

Numerous systems have been proposed to grade the severity of mucositis in an effort to standardize the reporting of clinical findings. To date, the two most commonly used scales include those developed by the National Cancer Institute and the World Health Organization.

NCI Scale	
Grade 0	None
Grade 1	Painless ulcers, erythema, or mild soreness in the absence of ulcers
Grade 2	Painful erythema, edema, or ulcers but eating or swallowing possible
Grade 3	Painful erythema, edema, or ulcers requiring IV hydration
Grade 4	Severe ulceration requiring parenteral or enteral nutritional support or prophylactic intubation
Grade 5	Death related to toxicity
WHO Grading Scale	
Grade 0	None
Grade 1	Soreness +/- erythema, no ulceration
Grade 2	Erythema, ulcers. Patients can swallow solid diet
Grade 3	Ulcers, extensive erythema. Patients cannot swallow solid diet
Grade 4	Oral mucositis to the extent that alimentation is not possible

*World Health Organisation. Handbook for reporting results of cancer treatment. 1997;pp.15-22.*

Virtually all patients will experience some degree of mucositis during radiation therapy. Oral rinsing may be helpful to soothe tissues. Patients should use a physiologic oral rinse with salt and water. Some of the rinses are commercially available while others can be made at home. Hydrogen peroxide can be used for debridement of ulcerated areas but should be avoided as a part of a daily rinse, as it can interfere with collagen formation and thus wound healing. Any removable prosthetic appliances should be removed during periods of mucositis. Oral lesions should be evaluated for Candida by Gram stain or KOH preparation or treated presumptively when yeast infection is suspected. Topical anesthetics and/or systemic pain medication are used for pain control.

### **Fungal Infections**

Candidal infections of the oral mucosa are common in patients undergoing radiation therapy and can cause a burning or scalded sensation, distort taste and interfere with swallowing. However in many patients no symptoms are reported, so thorough oral examination is imperative to detect these infections. These infections are easily treated if caught early. If not managed aggressively, oral infection has been shown to be a risk factor for spread to the esophagus.

Management of Candidal infections is critical and the condition is most easily treated when detected early. Gram stain or KOH wet prep can assist with diagnosis, but most clinicians feel it is reasonable to treat based on clinical findings. If patients with oral candidiasis complain of sore throat, esophageal candidiasis may also be present. Fluconazole tablets are the mainstay of treatment since oral troches must be used frequently (five times per day) and may be poorly tolerated by the patient with mucositis. Xerostomic patients may have difficulty dissolving troches or pastilles. Itraconazole suspension may be used if the patient has resistance to fluconazole. Nystatin suspension should be avoided due to sugar content and poor patient acceptance.

### **Post-Radiation**

Patients should be placed on 3 month dental recall after the completion of RT and the importance of oral hygiene and patient education cannot be overstated. The extent of xerostomia and any palliative/preventive measures should be evaluated.

Table 1: Mouthrinses

Mouth rinses	Composition/ Instructions for use:	Uses/Functions	Disadvantages
<b>Neutral rinse</b>	1/4 tsp. salt 1/4 tsp. baking soda 1 qt. H <sub>2</sub> O Use every 2 hours until soreness, nausea or ropy saliva contraindicate. Switch to 1/2 tsp. soda and 1 qt. water or water only, if necessary. Should not be swallowed	May be used during mucositis (omit salt) Neutralizes acids after emesis Dissolves thick, mucinous salivary secretions Soothing to irritated tissues Dislodges debris	None
<b>Saline rinse</b>	1/2 tsp. salt 8 oz. water	Not damaging to oral mucosa Helps reduce mucosal irritation Increases moisture in mouth Removes thickened secretions and debris Recommended for treatment of leukemic gingivitis and head and neck radiation	None
<b>Hydrogen peroxide</b>	Not recommended for use as a daily rinse Should be diluted 1:4 if used Do not use in the presence of blood clots, as this may promote bleeding Use to cleanse wounds prior to secondary medication/rinse Use for 1-2 days maximum Should be followed by therapeutic rinses	Helpful in periodontal infections when anaerobic microorganisms are involved	May delay wound healing Cause demineralization May promote emesis Causes dry mouth, thirst and discomfort Unpleasant taste

Table 2: Anti-fungals

Fluconazole (Diflucan <sup>®</sup> ) 100 mg tablets Disp: 8 to 15 tablets Sig: Take 2 tabs on day one and then one tab for 6 to 13 days (Oral suspension is also available in 10 mg/ml)
Clotrimazole (Mycellex <sup>®</sup> ) 10 mg troches Disp: 70 troches Sig: Dissolve one troche in the mouth five time per day for 14 days
Itraconazole (Sporonox <sup>®</sup> ) suspension 100 mg/10 ml Disp: 140-280 ml Sig: Swish and swallow 200 mg for 7 to 14 days
Nystatin (Mycostatin <sup>®</sup> ) 200 mg oral pastilles Disp: 56 pastilles Sig: Dissolve pastilles in mouth four times per day for 14 days

**Management of Trismus**

Vertical dimension of opening before/after radiation therapy should be maintained. Current options for maintaining and increasing vertical dimension include: tongue depressors taped together, Therabite<sup>®</sup> or Dynasplint<sup>®</sup>. Rigorous daily opening and closing exercises should be employed and warm moist heat applied before and after exercise. Anti-inflammatory drugs and muscle relaxants can be used as needed.

**Endodontics**

Cautious conservative endodontics can be performed if trismus does not preclude access. Instrumentation should not violate periapical tissues and extrusion of filling material beyond the apex should be avoided. Caustic agents should be avoided and access openings should never be left open. Durable temporary restorations should be placed. Periapical radiolucencies may not resolve in irradiated bone and periapical surgery should be avoided in these cases.

**Oral and Maxillofacial Surgery**

In preparation for oral surgical intervention in a post-radiation patient, the dental clinician should have a discussion with the treating radiation oncologist for the summary of radiation treatment. This includes gathering specific details on the treatment parameters that can ultimately affect the wound healing capacity such as dose and radiation ports for conventional radiation and isodose figures

## HEAD AND NECK RADIATION THERAPY

for IMRT. All patients requiring surgical intervention in an irradiated volume should have an informed consent signed with language including potential development of ORN. Pre-extraction HBO increases tissue oxygen saturation when dealing with irradiated bone, to enhance healing (especially in mandible). Typically 20 or more HBO treatments or “dives” can be done before surgery and 10 or more after surgery. Prophylactic preoperative antibiotic coverage is recommended, and surgery goals should include alveolectomy with primary closure.

### **Periodontics**

In management of periodontal disease it should be remembered that post-radiation patients are at increased risk for ORN and care must be taken to minimize tissue trauma. Flap surgery with or without osseous recontouring should be avoided. Hyperbaric oxygen (HBO) can be employed if surgical intervention is needed and the patient has received over 50 Gy of radiation to the area in question.

### **Prosthodontics**

Evaluation of mucosa should be undertaken before placement of dentures and 3-4 months should be allowed prior to the initiation of prosthetic rehabilitation. Implants may be considered 12-18 months following radiation therapy. HBO therapy may be necessary prior to surgical intervention, depending upon the amount of radiation the implant site has received. Doses of >50Gy may require HBO. Implant supported prosthesis should be placed when possible to reduce tissue trauma.

### **Osteoradionecrosis Management/Hyperbaric Oxygen Therapy**

Typical HBO management calls for 1 compression/decompression cycle per day five days per week. Patients who meet the definition of ORN begin with staged treatment as follows:

**Stage I** - If the wound shows definitive clinical improvement after 30 compression/decompression cycles, the patient is given a full course of 60 compression/decompression cycles. If there is no improvement after 30 compression/decompression cycles, the patient is advanced to stage II.

**Stage II** - A transoral alveolar sequestrectomy with primary closure is done and the compression/decompression cycles are resumed. If healing progresses without complication, a total of 60 compression/decompression cycles are completed. If there is incomplete healing, the patient is advanced to stage III.

**Stage III** - The patient undergoes a resection of the necrotic bone, the margins of which are determined by the presence of bleeding bone or by TCN fluorescence. Compression/decompression cycles are continued until healthy mucosal closure is obtained or a total of 60 compression/decompression cycles are given. The patient is then advanced to stage III-R. A patient can enter this stage directly if he/she presents with a pathologic fracture, orocutaneous fistula, or radiographic evidence of resorption to the inferior border. An initial course of 30 compression/decompression cycles are given in these cases.

**Stage III-R** - Ten weeks after resection, 20 additional compression/decompression cycles are given and bone graft reconstruction is accomplished from a transcutaneous approach.

### **COMBINED RADIATION AND CHEMOTHERAPY**

Historically chemotherapy was given only to patients with advanced head and neck cancer as a palliative treatment when surgery and radiation therapy had failed. However, the use of combined chemotherapy and radiation is now considered standard for most locally advanced tumors. This may be used for large tumors to preserve tissue where surgery would be too debilitating or for rapidly growing tumors with advanced nodal disease where cure with radiation therapy and surgery alone would be unlikely. Chemotherapy can be given as induction (prior to radiation therapy) or, more commonly, concomitantly with radiation therapy. The toxicities of this combined therapy are essentially the same as with radiation alone but they develop more rapidly and are typically more severe when they reach maximum level. Pre and post cancer therapy should be directed primarily to the radiation toxicities. Certain toxicities, such as infection, may be caused by chemotherapy. For example, these patients will be more immunosuppressed than those receiving radiation therapy alone. Therefore suspicion for oral infection should be high. These may include odontogenic infections, Candida infections, and herpes simplex infections. Refer to management of these infections in the chapter on Chemotherapy.

## XEROSTOMIA MANAGEMENT IN THE HEAD AND NECK RADIATION PATIENT

### INTRODUCTION

Hyposalivation is a devastating and consistent complication of head and neck radiation. A detailed description of the management of this condition is presented here. Much of this material would also apply to any patient experiencing xerostomia.

Ionizing radiation that includes the salivary glands results in acinar damage and cell death and affects the vascular elements of the glands with subsequent fibrosis of the salivary glands. Decreased salivary flow has been reported at doses of 10 Gy, while permanent hyposalivation may occur at doses greater than 25 Gy. A loss or significant reduction of salivary function is one of the most unpleasant and problematic side-effects of radiation therapy involving the head and neck. The major salivary glands produce approximately one liter of saliva per day. The average unstimulated flow rate is 0.4 ml/min and the average stimulated flow rate is 2.0 ml/min. The commonly accepted values for lower limits of normal salivary function are 0.1 – 0.2 ml/min unstimulated flow rate and 0.7 ml/min stimulated flow rate, although the definition of adequate salivary volume to prevent oral/dental disease and maintain comfort is not clearly defined. In addition to loss of salivary volume, changes in the constituents of saliva and changes in viscosity impact salivary function. When salivary production is compromised most individuals experience the sensation of a dry mouth, which is termed xerostomia. Loss of salivary function leads to a plethora of adverse sequelae, including:

- Alteration/reduction in taste function
- Difficulty with chewing, bolus preparation and swallowing
- Esophageal dysfunction, including chronic esophagitis
- Nutritional compromises
- Higher frequency of intolerance to oral medications and oral care products (lack of buffering)
- Increased incidence of local/regional infection (glossitis, candidiasis, dental caries, halitosis, bacterial sialadenitis)
- Loss of oral buffering capacity
- Reduction in remineralizing capacity leading to dental sensitivity and markedly increased susceptibility to dental caries
- Decreased resistance to loss of tooth structure due to attrition, abrasion and erosion (corrosion)
- Increased susceptibility to mucosal injury
- Inability to wear dental prostheses

The increased susceptibility to caries caused by hyposalivation and changes in saliva often results in rampant caries involving teeth both within and outside of the fields of radiation. Rampant caries can result in an increased risk of osteoradionecrosis. Reduced saliva volume and increased viscosity of the secretion can also result in difficulty sleeping due to oral dryness waking the patient during the night. The annoying problem of dealing with a constantly dry mouth can result in a loss of social and physical well-being. It can also become an emotional challenge with the possible result of withdrawal and clinical depression.

Managing the oral health of patients with radiation-induced xerostomia can be extremely challenging for the dentist. The following statement made by Dr. Ira Shannon in 1977 concerning these patients holds true today: “The maintenance of oral health in xerostomic patients is demanding for both the patient and the dentist. It requires cooperation and compliance on the part of the patient, with a commitment of time and effort well beyond that required for normal oral care. The dentist must promote and inspire this cooperation, provide detailed instructions and guidance, and follow the patient meticulously. Only in this way can the ravaging form of caries often found in these patients be prevented.”

The management of head and neck radiation therapy patients with xerostomia should begin prior to the patient receiving head and neck radiation therapy. The past performance of the patient regarding oral hygiene and the value placed on their dentition is a reliable predictor of future results. Patients who have not taken good care of their dentition prior to head and neck radiation therapy are unlikely to take good care of their dentition following radiation therapy. When it is predictable that these patients will have very little salivary function remaining following head and neck radiation therapy, it is appropriate to extract teeth located within the high dose radiation volume prior to radiation therapy, and while all teeth will be at risk of dental disease in a patient with hyposalivation, teeth outside of the high dose radiation volume can be managed by extraction after cancer therapy. However, preventive management should be instituted and reinforced to reduce the burden of dental disease.

During radiation therapy, as normal meals become more difficult to ingest, patients may adopt a more cariogenic diet and sometimes use a cariogenic beverage to repeatedly moisten the mouth. When managing dentate patients with hyposalivation, it is very important to educate the patient regarding the effects radiation will have on their saliva and teeth. They must understand that reduced salivary flow places them at a greatly increased risk for dental caries, which cannot be controlled without their cooperation.

## XEROSTOMIA MANAGEMENT

The provider must ensure that the patient understands the following requirements to maintain their dentition:

- Avoid moistening their mouth with cariogenic liquids such as soft drinks, citrus flavored or carbonated water, juices, punches, tea or any other liquid containing sugar.
- Avoid using any liquid with an acidic pH as a mouth moistener.
- Avoid using items containing sugar to stimulate salivary flow such as gums, mints, candies, lemon drops, etc.
- Avoid frequent between-meal snacks that contain large amounts of sugar.
- Understand the difference between sugar-free and sugar-less products. Only the former do not contain sugar and should be used by dry mouth patients. Sugar-less products do contain sugar – just less than a regular formulation.
- Perform thorough oral hygiene measures using a soft toothbrush and floss or a Proxabrush<sup>®</sup> (if sufficient space exists), and a fluoridated toothpaste (1100 ppm fluoride ion) at least twice per day.
- Brush teeth after every meal or snack.
- Use a topical fluoride rinse or gel daily. Patients should understand that the best method of providing daily topical fluoride treatments to the teeth is with a fluoride tray and a 1%-1.1% neutral sodium fluoride gel. They must understand that over-the-counter fluoride rinses are much less effective than prescription fluoride gels and rinses.
- Commit to follow-up dental examinations every three months during the first year and from every three to six months thereafter depending on their oral condition.

The provider must also ensure that the patient understands that, due to their decreased salivary flow, they have lost most or all of their saliva's protective functions, which include:

- The formation of a pellicle to act as a physical barrier to the invasion of microorganisms and as a moisturizing lubricant to prevent abrasive tooth wear and soft tissue trauma.
- Potent antimicrobial effects, which help protect against bacteria, fungi and viruses in the mouth.
- A washing effect to help clear the oral cavity of microorganisms and food debris, especially sugars.
- A hydrating effect that moistens the mouth and aids in chewing and swallowing.
- The promotion of remineralization of the teeth because saliva is a saturated solution of calcium and phosphate ions.
- A high buffering capacity, which protects the dentition against acids from both external and internal sources and aids in the control of the microorganisms that are responsible for dental decay and oral fungal infections.

## MANAGEMENT

### *Topical Management of Dry Mouth Discomfort*

Over-the-counter sugar-free gums and mints are safe to use to stimulate any remaining salivary function; however, xylitol-containing gums and mints are preferable because xylitol inhibits the growth of cariogenic bacteria (mutans streptococci) that cause tooth decay (Table 3). There are several proprietary products that claim to increase salivary flow; however, they are more expensive than over-the-counter sugar-free gums and mints and evidence that they are more beneficial is lacking.

There are numerous commercial salivary substitutes available (Table 4), however these are used for palliation and stimulation of residual function should be considered prior to a palliative approach. There are few comparative trials of mouth-wetting agents, and several of these products have been found to have a pH below 5.1. Studies have found that saliva substitutes with a pH of 5.1 or less lead to demineralization and loss of tooth structure unless they contain calcium and phosphate ions and/or fluoride ions. Studies have found that carboxymethylcellulose-based saliva substitutes with a saturation of 3.2 with respect to octacalciumphosphate and a pH of 6.5 enable the solution to remineralize bovine enamel in vitro. Presently there is no ideal salivary substitute commercially available. Because saliva substitutes are somewhat expensive, and have a short duration of action, many patients prefer to use water to moisten their mouth. Because of the confirmed topical benefit of fluoridated water, patients should use water known to contain approximately 1 ppm fluoride as a mouth moisturizer. Commercially available bottled water does not usually contain significant amounts of fluoride and some home water purification systems remove the fluoride that is present in tap water. Patients should be encouraged to use unfiltered fluoridated tap water as a mouth moistener.

The Biotene<sup>®</sup> products from Laclede are formulated for dry mouth patients and comparative trials have shown patient satisfaction with these products. These products contain natural salivary enzymes and proteins as well as xylitol. The potential benefits of the presence of salivary enzymes in vivo are not well documented. Biotene<sup>®</sup> toothpaste does not contain sodium lauryl sulfate and Biotene<sup>®</sup> mouthwash does not contain alcohol, both of which can be irritating to dry mouth patients. Oralbalance Moisturizing Gel<sup>®</sup> is another Biotene<sup>®</sup> product that has met with patient acceptance. It is a clear viscous water-soluble gel that contains xylitol as well as natural salivary enzymes and proteins. It can be used to coat oral soft tissues to protect and lubricate them. It has a longer

duration of action than water and many patients find it beneficial to use when they need something that lasts longer than fluoridated water, e.g., in the evening prior to going to sleep.

TheraSpray<sup>®</sup> from Omni Preventive Care is another product that may be considered for symptomatic relief of a dry mouth. It contains a silicone molecule (poloxamer 407), which has an affinity for mucosa. It has a neutral pH and provides longer lasting relief from oral dryness than water. Some patients prefer to use it in place of Oralbalance Gel<sup>®</sup> prior to retiring in the evening as well as using it throughout the day.

*Table 3 Gums and Mints*

PRODUCTS CONTAINING XYLITOL	MANUFACTURER	TELEPHONE
B-Fresh <sup>®</sup> Xylitol Mints	B-Fresh Johnston, RI www.bfreshgum.com	800-555-1276
Biotene <sup>®</sup> Dry Mouth Gum	Laclede, Inc. Rancho Dominguez, CA www.laclede.com	800-922-5856
Smint <sup>®</sup> Gum	Perfete van Melle Lainati, Italy www.smint.com	34 93 495 2727
Smint <sup>®</sup> Mints	Perfete van Melle Lainati, Italy www.smint.com	34 93 495 2727
Spry <sup>™</sup> Gum	Xlear Inc. Orem, UT www.xlear.com	877-599-5327
Spry <sup>™</sup> Mints	Xlear Inc. Orem, UT www.xlear.com	877-599-5327
TheraGum <sup>®</sup>	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN http://solutions.3m.com/	800-634-2249
TheraMints <sup>®</sup>	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN http://solutions.3m.com/	800-634-2249
Trident <sup>®</sup> Gum (but not Trident White or Splash)	Cadbury Adams USA LLC Parsippany, NJ www.tridentgum.com	800-874-0013
Trident Xtra Care <sup>™</sup> Gum Also contains Recaldent <sup>®</sup> (casein phosphopetide-amorphous calcium phosphate for remineralization)	Cadbury Adams USA LLC Parsippany, NJ www.tridentgum.com	800-874-0013
Xponent <sup>®</sup> Xylitol Gum	Global Sweet Polyols LLC Rehoboth, MA www.globalsweet.com	800-601-0688
Xponent <sup>®</sup> Xylitol Mints	Global Sweet Polyols LLC Rehoboth, MA www.globalsweet.com	800-601-0688

## XEROSTOMIA MANAGEMENT

Table 4 Mouth-wetting agents

PRODUCT	MANUFACTURER	TELEPHONE
Biotene® Moisturizing Mouth Spray pH 7.0, Bio-active enzymes, amino acids, milk proteins	Laclede Inc. Rancho Dominguez, CA www.laclede.com	800-922-5856
BioXtra® Moisturizing Gel Milk proteins, salivary enzymes	Bio-X Healthcare Gembloux, Belgium www.bioxhealthcare.com	32 (0)81 72 34 65
BioXtra® Gel Mouthspray Milk proteins, salivary enzymes	Bio-X Healthcare Gembloux, Belgium www.bioxhealthcare.com	32 (0)81 72 34 65
Caphoso® (Rx) High concentration calcium and phosphate ions	Cytogen Corp Princeton, NJ www.cytogen.com	800-833-3353
Moi-Stir® Oral Spray pH 7.0 (carboxymethylcellulose), sorbitol, glycerin	Kingswood Laboratories Indianapolis, IN	800-968-7772
Numoisyn® Liquid Rx only – contains linseed extract, methylparaben and propylparaben	Align Pharmaceuticals Cary, NC www.alignpharma.com	919-398-6225
Oasis® Mouthwash & Spray 35% glycerin oral demulcent	GlaxoSmithKline Brentford, United Kingdom www.gsk.com	888-825-5249
Oral Balance® Moisturizing Gel pH 6.0, Xylitol sweetener, Bio-active enzymes in a hydroxymethylcellulose base	Laclede Inc. Rancho Dominguez, CA www.laclede.com	800-922-5856
Oral Balance® Liquid pH 7.0, Xylitol, Bio-active enzymes, 8 amino acids, milk proteins	Laclede Inc. Rancho Dominguez, CA www.laclede.com	800-922-5856
Saliva Substitute® pH 6.5 (carboxymethylcellulose), sorbitol, mild mint flavor	Roxane Laboratories Inc. Columbus, OH www.roxane.com	800-962-8364
Salivart® Synthetic Saliva pH 6.0-7.0 (carboxymethylcellulose)	Gebauer Company Cleveland, OH www.gebauerco.com	800-321-9348
Thayers® Dry Mouth Spray (Citrus)] pH 6.0, Glycerin, tris amino, lemon/lime flavor	Thayers Natural Pharmaceuticals Westport, CT www.thayers.com	888-842-9371
TheraSpray® pH 7.0, 1.2% poloxamer 407/dimeticone, xylitol	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN http://solutions.3m.com/	800-634-2249
VA OraLube pH 7.0xylitol, 2 ppm F (carboxymethylcellulose)	Only available from VA Hospitals NDC 052859-005	

Note: Oral moisturizers/artificial saliva having a pH < 5.5 are not recommended. Examples include MouthKote®, Stoppers 4 Dry Mouth Spray®.

### Systemic Management of Dry Mouth Discomfort

Stimulation of saliva production should always be considered prior to palliation due to the critical role of salivary constituents in maintaining homeostasis in the oral environment. It is valuable to determine if residual salivary function remains by measuring the salivary flow rate, prior to prescribing a systemic sialogogue. If there is no measurable saliva following the collection of resting and stimulated saliva, systemic sialogogues are unlikely to be effective. If there is measurable saliva, sialogogues should be considered. Available agents in the United States are: Salagen® (pilocarpine), Evoxac® (cevimeline) and Bethanechol® (urecholine). These are acetylcholine analogues that stimulate exocrine glands via their actions as agonists at muscarinic receptor sites. Salagen® (pilocarpine) is a nonselective muscarinic agent which affects both the M3 receptors in the exocrine glands as well as the M2 receptors in the heart and has a duration of action of approximately 3 hours. It is available in 5 and 7.5 mg tablets and the recommended dose is 5 -10 mg t.i.d. (not to exceed 30 mg per day). It has been approved by the FDA for relief of symptoms of dry mouth secondary to Sjögren's syndrome and for dry mouth secondary to radiation therapy. Evoxac® (cevimeline) may have greater affinity for the M3 receptors in the glands and a lower affinity for the M2 receptors on the heart (fewer rhythmogenic cardiac effects), although this difference has not been proven in clinical trials. It has a longer duration of action due to plasma protein binding capacity (approximately 5 hours.) It is available as a 30 mg tablet and the recommended dose is 30-60 mg t.i.d (not to exceed 180 mg per day). It has been approved by the FDA for symptoms of dry mouth secondary to Sjögren's syndrome and for dry mouth secondary to radiation therapy. Bethanechol has been used off label and like cevimeline, may have a longer half-life. Doses range from 10-75 mg t.i.d., with most using 25 mg t.i.d. Comparative trials have been conducted of these agents.

Pilocarpine is also available as an ophthalmic solution. It is available in a variety of concentrations and comes in 15 ml dropper bottles. The 1% solution can be prescribed with instructions to place 1/2 ml - 1 ml on the tongue t.i.d. not to exceed 3 ml per day. Another option is a 4% solution, which should be diluted to 600 ml with tap water to create a 1 mg/ml solution. The patient is instructed to take 5-10 ml (1-2 teaspoons) t.i.d. not to exceed 30 ml per day. The advantage of prescribing pilocarpine in a solution form is that it is much less expensive, however, the solution is rapidly absorbed and the dose taken more difficult to control. Caution should be used in prescribing ophthalmic solution and dosing should be monitored closely, as overdosing has been reported.

All the sialogogues have similar unwanted side effects. The most common are: gastrointestinal upset, sweating, tachycardia, increased pulmonary secretions, increased smooth muscle tone and blurred vision, especially at night. Caution should be advised while driving at night or performing hazardous activities in reduced lighting. In addition, they have similar contraindications that include: gall bladder disease, narrow-angle glaucoma, acute iritis, uncontrolled asthma, known hypersensitivity to the drug, and renal colic. Pilocarpine and cevimeline have similar warnings and precautions. Risks to the patient must be considered when administering either medication to individuals with cardiovascular disease, controlled asthma, angina pectoris, chronic bronchitis, chronic obstructive pulmonary disease, or a history of myocardial infarction, nephrolithiasis or cholelithiasis. Drug interactions may include: beta-blockers, other parasympathomimetic drugs, and medications that have a significant affect on the cytochrome P450 liver enzyme system.

**Table 5 Rx Sialogogues**

PRODUCT	MANUFACTURER	TELEPHONE
Bethanechol, 25 mg tablets (generic)	Global Pharmaceuticals Chalfont, PA www.globalphar.com	215-933-0323
Evoxac® (Cevimeline HCl) 30 mg capsules	Daiichi Sankyo Parsippany, NJ www.daiichius.com	877-437-7763
Pilocarpine Hydrochloride Tablets, 5 mg Equivalent to Salagen®	Roxane Laboratories Columbus, OH www.roxane.com	800-962-8364
Pilocarpine Ophthalmic solution 15 ml (4% solution – 40mg/ml) dilute to 600 ml to create 1 mg/ml.	Available from local pharmacies	
Salagen® Tablets (Pilocarpine HCl) 5 mg tablets	MGI Pharma, Inc. Bloomington, MN www.mgipharma.com	800-562-5580

**Prevention and Treatment of Dental Caries**

In a dentate patient with hyposalivation, the lack of salivary oral clearance, remineralization action, buffering capacity and antibacterial activity may promote rampant dental caries. Normal salivary pH is approximately 6.8 - 7.2. In patients with reduced saliva production, the oral pH can fall into the acidic range. Hyposalivation promotes the rapid growth of acidophilic organisms such as mutans streptococci, lactobacillus and candida. It is critical that the treatment of dental caries follow a medical model as described by Anderson, Bales and Omnell. Using this model, dental caries is primarily approached as an infection of the oral cavity with treatment directed at the causative organism. This medical model must include the following:

- Manage hyposalivation
- Reinforce excellent oral hygiene
- Dietary instruction
- Eliminate existing mutans streptococci nidi of infection by removing caries from all cavitated caries lesions and obturating with glass ionomer interim restorations as well as sealing all carious pits and fissures.
- Initiate antimicrobial therapy using a 0.12% chlorhexidine rinse (Table 6). Instruct the patient to use ½ oz... oral rinse for one minute twice daily for two weeks. This will reduce the number of mutans streptococci below a pathological level for 12 - 36 weeks in non-cancer patients. However, studies in head and neck cancer patients document rapid recolonization when chlorhexidine is discontinued, which is in contrast to studies of non-cancer patients and therefore continuing use and compliance is of increased importance in cancer patients. Attempts to reduce the exposure to chlorhexidine (i.e., ½ oz.. for one minute twice daily one or two days per week) must be undertaken with caution and closely monitored.

## XEROSTOMIA MANAGEMENT

*Table 6 Rx Chlorhexidine Mouthrinses - 0.12% Chlorhexidine Gluconate, 11.6% Alcohol*

PRODUCT	MANUFACTURER	TELEPHONE
Denti-Care® Oral Rinse	Medicom USA Tonawanda, NY www.medicom.ca	800-308-6589
Peridex®	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN http://solutions.3m.com/	800-634-2249
PerioGard®	Colgate Oral Pharmaceuticals New York, NY www.colgateprofessional.com	800-372-4346
PerioRx®	Discus Dental Culver City, CA www.discusdental.com	800-422-9448
Pro-DenRx® 0.12% Chlorhexidine Rinse	Pro-Dentec Batesville, AK www.prodentec.com	800-228-5595

*Table 7 Fluoride Varnishes - 5% Sodium Fluoride - 22.6 mg/ml F, 22,600 ppm F*

PRODUCT	MANUFACTURER	TELEPHONE
CariFree® - Single dose syringes volume not specified	Oral BioTech Albany, OR www.carifree.com/dentists	866-928-4445
CavityShield® - Unit dose 0.25ml and 0.4 ml	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN http://solutions.3m.com/	800-634-2249
Duraflor® - 10ml Tube	Medicom USA Tonawanda, NY www.medicom.ca	800-308-6589
Duraflor® - Unit dose 0.25ml and 0.4ml	Medicom USA Tonawanda, NY www.medicom.ca	800-308-6589
Duraflor® Halo White Varnish Unit dose – 0.5ml	Medicom USA Tonawanda, NY www.medicom.ca	800-308-6589
Duraphat® - 10ml Tube Prevident® Varnish - Unit dose - 0.4ml transparent on teeth	Colgate Oral Pharmaceuticals, Inc. Canton, MA www.colgateprofessional.com/	800-372-4346
DuraShield® - Unit dose – 0.4ml	Sultan Healthcare Englewood, NJ www.sultanintl.com	800-637-8582
Enamel Pro® Varnish - Unit dose 0.25ml and 0.4ml - Dries white Contains Amorphous Calcium Phosphate	Premier Dental Plymouth Meeting, PA www.premusa.com/dental	888-670-6100
Flor-Opal® - Unit dose 0.5ml Syringes Contains Xylitol	Ultradent South Jordan, UT www.ultradent.com	888-230-1420
FluoroDose® - Unit dose - 0.3ml Translucent A-2 shade	Centrix Shelton, CT www.centrixdental.com	800-235-5862
Fluorilaq – 10ml Tube	Pascal Company, Inc. Bellevue, WA www.pascaldental.com	800-426-8051
Nupro® 5% Sodium Fluoride Varnish Unit dose - volume not specified	Dentsply International York, PA www.dentsply.com	800-877-0020
Varnishamerica™ - Unit dose 0.25ml and 0.4ml Contains Xylitol Dries to a natural tooth color	Medical Products Laboratories Philadelphia, PA www.medicalproductslaboratories.com/public-health/varnishamerica.html	800-523-0191
*Unit dose packaging preferred; content per dose may vary with tube packaging.		

While the effect of fluoride varnish has not been studied in cancer patients, (Table 7) it may be reasonable to consider the use of 1% neutral sodium fluoride gel such as FluoriSHIELD® or Preident® in medication trays or when not possible as a brush-on (Tables 7 & 8) to protect the teeth against demineralization and promote remineralization. Consideration should be given to use of calcium and phosphate products, as remineralization requires their presence in the environment in order to reduce demineralization and promote remineralization.

Fabricate fluoride trays for the application of the neutral sodium fluoride gel (ideally this should be done prior to radiation therapy). Both 1-1.1% neutral sodium fluoride and 0.4% stannous fluoride gels have proven effective. However, stannous fluoride is highly acidic and may affect certain types of restorations, especially glass ionomers. Neutral sodium fluoride is the agent of choice for patients with glass ionomer restorations. Instruct the patient on the daily use of the trays as follows:

- Place a ribbon of 1%-1.1% neutral fluoride gel in the carriers
- Insert both the upper and lower carrier
- Gently bite several times to “pump” gel between the teeth
- Leave the carriers in place for 5 to 10 minutes
- Remove carriers and expectorate the gel but do not rinse
- Rinse the carriers and allow to air dry
- Do not eat or brush for at least 30 minutes (optimal time to use is prior to bedtime)

*Table 8 Fluoride Gels - 1.1% Sodium Fluoride, 5000 ppm, pH 7.0*

PRODUCT	MANUFACTURER	TELEPHONE
ControlRx™	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN <a href="http://solutions.3m.com/">http://solutions.3m.com/</a>	800-634-2249
Denti-Care® Sodium fluoride Gel	Medicom USA Tonawanda, NY <a href="http://www.medicom.ca">www.medicom.ca</a>	800-308-6589
FluorideX®	Discus Dental Culver City, CA <a href="http://www.discusdental.com">www.discusdental.com</a>	800-422-9448
FluoriSHIELD®	Medical Products Laboratories Philadelphia, PA <a href="http://www.medicalproductslaboratories.com">www.medicalproductslaboratories.com</a>	800-523-0191
NeutraCare®	P & G Cincinnati, OH <a href="http://www.oralbprofessional.com">www.oralbprofessional.com</a>	800-543-2577
NeutraGard® Home Care Gel	Pascal Company, Inc. Bellevue, WA <a href="http://www.pascaldental.com">www.pascaldental.com</a>	800-426-8051
Preident®	Colgate Oral Pharmaceuticals New York, NY <a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>	800-372-4346
Pro-DenRx® Neutral Sodium Brush-On Gel	Pro-Dentec Batesville, AK <a href="http://www.prodentec.com">www.prodentec.com</a>	800-228-5595
Topex® Take Home Care®	Sultan Dental Products Englewood, NJ <a href="http://www.sultandental.com">www.sultandental.com</a>	800-637-8582
*The 0.4 SnF2 gels such Gel-Kam® and Omni-Gel® are not recommended because of their acidity (pH 2.4-4.7) and lower fluoride concentration (1000 ppm) vs. 1-1.1% NaF (pH 7.0, 5000 ppm F).		

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Table 9 Fluoride Toothpastes - 1.1% Sodium Fluoride, 5000 ppm, pH 7.0

PRODUCT	MANUFACTURER	TELEPHONE
ControlRx™	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN <a href="http://solutions.3m.com/">http://solutions.3m.com/</a>	800-634-2249
ContolRX™ Sodium fluoride Dentifrice	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN <a href="http://solutions.3m.com/">http://solutions.3m.com/</a>	800-634-2249
FluorideX Daily Defense®	Discus Dental Culver City, CA <a href="http://www.discusdental.com">www.discusdental.com</a>	800-422-9448
NeutraGard® Advanced Home Care Gel with Dentifrice	Pascal Company, Inc. Bellevue, WA <a href="http://www.pascaldental.com">www.pascaldental.com</a>	800-426-8051
Prevident 5000 Plus®	Colgate Oral Pharmaceuticals New York, NY <a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>	800-372-4346
Prevident 5000 Booster®	Colgate Oral Pharmaceuticals New York, NY <a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>	800-372-4346
Prevident® 5000 Dry Mouth SLS free formulation	Colgate Oral Pharmaceuticals New York, NY <a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>	800-372-4346
Prevident® 5000 Sensitive 5% potassium nitrate	Colgate Oral Pharmaceuticals New York, NY <a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>	800-372-4346
Pro-DenRx® Plus Neutral Brush-On Dentifrice	Pro-Dentec Batesville, AK <a href="http://www.prodentec.com">www.prodentec.com</a>	800-228-5595

Table 10 Fluoride Mouthrinses

Rx PRODUCTS - Neutral pH, 0.2% NaF, 900 ppm	MANUFACTURER	TELEPHONE
CaviRinse®	Omni Preventive Care 3M ESPE Dental Products St. Paul, MN <a href="http://solutions.3m.com/">http://solutions.3m.com/</a>	800-634-2249
Dental Resources Neutral Gel	Dental Resources, Inc. Delano, MN <a href="http://www.dentalresourcesinc.com">www.dentalresourcesinc.com</a>	800-328-1276
Oral-B® Fluorinse®	P & G Cincinnati, OH <a href="http://www.oralbprofessional.com">www.oralbprofessional.com</a>	800-543-2577
Prevident® Dental Rinse	Colgate Oral Pharmaceuticals New York, NY <a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>	800-372-4346
Pro-DenRx® Neutral Rinse	Pro-Dentec Batesville, AK <a href="http://www.prodentec.com">www.prodentec.com</a>	800-228-5595
The 0.2% NaF rinses (900 ppm F) are an acceptable alternative for patients who will not use the 1.0-1.1% NaF gels, although more expensive and not as effective.		
OTC PRODUCTS - 0.05% NaF, 225 ppm	MANUFACTURER	TELEPHONE
Act® Fluoride Rinse pH 5.8 – 6.6, 0.05%, Alcohol Free	Chattem, Inc Chattanooga, TN <a href="http://www.actfluoride.com">www.actfluoride.com</a>	866-228-7467
Fluorigard®	Colgate Oral Pharmaceuticals New York, NY <a href="http://www.colgateprofessional.com">www.colgateprofessional.com</a>	800-372-4346
Oral-B® Anti-Cavity Rinse Alcohol Free	P & G Cincinnati, OH <a href="http://www.theessentials.com">www.theessentials.com</a>	800-924-4950
The 0.05% NaF rinses do not equally replace the daily use 1.0-1.1% NaF gels because of their much lower fluoride concentration (225 ppm F). If these low concentration rinses are used, they should be alcohol free. The 0.63% SnF <sub>2</sub> rinses such as PerioMed® or Gel-Kam Rinse® are not recommended because their fluoride concentration is low (dilute to 0.1% SnF <sub>2</sub> = 250 ppm F) and they are very acidic (pH - 2.8-3.5). The APF rinses such as Phos-Flur® are not recommended because of their acidic pH 4.0.		

Low concentration products such as 0.05% (250 ppm) sodium fluoride rinses (Table 10) and 0.63% stannous fluoride rinses (diluted 1:8 - 250 ppm) have not been shown to be effective in dry mouth patients. The most effective products are those containing 5000 ppm such as the 1%-1.1% sodium fluoride gels and toothpastes. The recommended technique is a 1%-1.1% sodium fluoride gel in fluoride trays, together with the twice-daily use of a conventional 1100 ppm sodium fluoride toothpaste. The next most favorable protocol is to brush on the sodium fluoride gel, together with the twice-daily use of a conventional 1100 ppm sodium fluoride toothpaste.

Begin definitive restorative therapy when the above approaches to dental demineralization have been addressed, with direct restorative materials. Resin modified glass ionomer restorations are the materials of choice to restore class 3 and class 5 preparations due to their antibacterial surface properties and their proven ability to afford some protection from recurrent caries at the cavosurface restorative margins. In higher stress areas, such occlusal and incisal surfaces, either composite resin or amalgam can be used. Compomer materials are not recommended because of their need to be replaced more frequently due to recurrent caries, as well as their inferior physical properties as compared to amalgam or composite resin. Consideration should be given to using an “open sandwich” technique when placing either amalgam or composite resin on the root surfaces of these patients. Restorative recommendations are as follows:

### ***Patients Compliant with the Use of Topical Fluorides***

#### **Class 1 or 2 Direct Restorations**

- Either amalgam or microhybrid composite

#### **Class 3 Direct Restorations**

- Either microhybrid composite or resin modified glass ionomer

#### **Class 5 Direct Restorations**

- Either amalgam, microhybrid composite or resin modified glass ionomer

#### **Laboratory Fabricated In-direct Restorations**

- Only after caries free for at least 6 months

#### **Enamel “White Spot” or Non-cavitated Dentin Lesions**

- Apply a fluoride varnish 2-3 times in one week, if possible
- Daily topical 1.0%–1.1% neutral sodium fluoride in trays 5-10 minutes

Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) is a non-fluoride agent developed at Melbourne University in Australia, which in some studies has been found to suppress tooth demineralization while enhancing tooth remineralization. These studies have shown that this material buffered plaque pH by stabilizing and localizing amorphous calcium phosphate within the plaque, thereby helping to maintain a state of supersaturation with respect to tooth enamel. In one study the buffering of the plaque resulted in a depression of demineralization and enhancement of remineralization as much as 63.9% (+/- 20%). Another study demonstrated that sugar-free gum is a safe and effective way to deliver CPP-ACP in order to promote remineralization of enamel in subsurface lesions. CCP-ACP is marketed as Recaldent<sup>®</sup> and in the United States it is commercially available in paste form as MI Paste<sup>™</sup> and MI Paste Plus<sup>™</sup> (CPP-ACP plus 0.2% NaF, 900 ppm) from GC America (Table 11). In other global markets it is marketed as GC Tooth Mousse. In addition to being marketed as a remineralizing agent it is also marketed as a desensitizing agent for exposed roots. In the United States Recaldent<sup>®</sup> is also available in Trident<sup>®</sup> Xtra Care<sup>™</sup> chewing gum (in other global markets it is available as Recaldent<sup>®</sup> Chewing Gum). The artificial saliva product CAPHOSOL<sup>®</sup>, available by prescription, also contains calcium and phosphate solution.

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**Table 11 Remineralizing Products**

PRODUCT	MANUFACTURER	TELEPHONE
CAPHOSOL® (Rx) High concentration calcium and phosphate ions	Cytogen Corp Princeton, NJ www.cytogen.com	800-833-3353
MI Paste™ Contains Recaldent™ (CPP-ACP), pH 7.	GC America Alsip, IL www.gcamerica.com	800-323-7063
MI Paste Plus™ Contains Recaldent™ (CPP-ACP) plus 0.2% NaF, 900 ppm, neutral pH	GC America Alsip, IL www.gcamerica.com	800-323-7063

### **Patients Not Compliant with the Use of Topical Fluorides**

- Provide dental care to control dental damage
- Class 1 and 2 Direct Restorations
  - Amalgam – glass ionomer liner may be beneficial
  - Composites not recommended
- Class 3 and 5 Direct Restorations
  - Resin modified (dual cure) glass-ionomer or packable (chemical cure) glass-ionomer
  - Composites not recommended
- Laboratory Fabricated In-direct Restorations - Not recommended
- Enamel “White Spot” or non-cavitated dentin lesion
  - Place a topical fluoride varnish as often as possible, but expect to restore early
  - Initially, close follow-up every 3 months assessing for caries
  - Careful examination and bite-wing radiographs until at least six months without lesions, may then extend time between follow-up appointments.
- Reinforce oral hygiene instructions and use of topical fluorides, chlorhexidine rinses and salivary stimulating agents

### **Prevention and Treatment of Candidiasis**

In patients with hyposalivation, the oral mucosa often becomes dry, sticky, rough, may bleed easily and is more susceptible to infection. The most frequently encountered mucosal infection associated with hyposalivation is candidiasis. A significant correlation between hyposalivation and *Candida* has been confirmed by Navazesh, et al. and shown in head and neck cancer patients with colonization and infection increasing during and following radiation therapy. Ramirez-Amador, et al. found that in this group of patients, candida colonization significantly increased from the initiation of therapy (43%) to the completion (62%) and continued to increase during follow-up visits to a prevalence of 75%. A shift in the species of the candida organisms from 85% *Candida albicans* at the beginning of radiation treatment to 65% at the termination of treatment was also noted, as was an increase in populations of other candidal species, including *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. cerevisiae*, and *C. krusei*.

*Candida* organisms have been found to colonize 67.9% of patients with self-reported xerostomia, of which 58% were found to have hyposalivation. The dry mouth patient's oral mucosa should be carefully examined for the infection. It may present as a pseudomembranous form (thrush), as an atrophic (erythematous) form (often associated with a removable dental appliance) or, less commonly as a hypertrophic (white) form. It should also be suspected when dry mouth patients complain of a burning mouth or tongue. At times this infection may spread to involve the commissures of the mouth, a condition described as angular cheilitis or cheilosis.

A clinical diagnosis of *Candida* may be supported by performing a Gram stain or potassium hydroxide (KOH) preparation from oral scrapings, especially with the pseudomembranous form, or confirmed with a fungal culture. There are several antifungal agents effective against *Candida albicans* as topical preparations and systemic medications (Table 12). Nystatin solutions contain large amounts of sucrose (approximately 50%), and should be avoided in dentate dry mouth patients. Dry mouth patients are often poorly compliant in the use of troches and pastilles because they lack sufficient saliva to dissolve them, which may also cause mucosal abrasion. Topical medications can be applied in creams applied to denture surfaces or lozenges or rinses. Systemic treatment may be more convenient. Systemic agents include ketoconazole (Nizoral®), fluconazole (Diflucan®) and itraconazole (Sporanox®). They are effective and do not require as frequent dosing as topical agents. Dosing frequency is important because compliance can be a significant problem when treating patients for fungal infections. Hyposalivation is thought to be a factor in response to fluconazole

because its salivary concentration is equal to its plasma concentration and systemic use may lead to both systemic and topical exposure in those with saliva production. However, fluconazole has been found to be effective in dry mouth patients. Fluconazole, because of its efficacy and excellent safety profile, is the recommended systemic therapy for oral candidiasis. However, development of resistance to fluconazole is a recognized problem and other species may have greater resistance. Itraconazole solution is a good alternative if this occurs. Itraconazole is also available as a solution and acts both as a topical and systemic medication. It has the advantage of containing no sugar (sweetened with sorbitol and saccharin), however, it has more liver toxicity than does fluconazole. Chlorhexidine gluconate also inhibits the growth of *Candida*, and may be useful in prevention and assist in reducing colonization, but is not recommended as a primary treatment against clinical infection.

**Table 12 Antifungal Products**

GENERIC	PROPRIETARY	DIRECTIONS
Clotrimazole cream	Lotrimin <sup>®</sup> , Mycelex <sup>®</sup> (1%)	Apply to affected area q.i.d.
Clotrimazole oral troches	Mycelex <sup>®</sup> Troches 10 mg	Let one troche dissolve in mouth 5 x / day
Fluconazole tablets*	Diflucan <sup>®</sup> 100 mg tabs	200 mg stat p.o., then 100 mg q.d. p.o..
Ketoconazole cream	Nizoral <sup>®</sup> 2%	Apply to affected area q.i.d.
Miconazole cream, powder	Monistat <sup>®</sup> 2%	Apply to affected area q.i.d.
Nystatin cream, ointment, powder	Mycostatin <sup>®</sup> cream, powder 100,000 units/gram	Apply to affected area q.i.d.
Nystatin solution**	Mycostatin <sup>®</sup> 100,000 units/ml	4-6 ml swish x 2 min & swallow q.i.d.
Nystatin oral pastilles	Mycostatin <sup>®</sup> 200 mg pastilles	Let one pastille dissolve in mouth 4 x day
Itraconazole solution*	Sporanox <sup>®</sup> Oral Solution 100 mg/10ml	10 ml swish and swallow bid
* Caution with drug interactions when using the azoles systemically. Check drug reference.		
** Not recommended because of the high sucrose content and need to use at least 4X day		

**Systemic Treatment of Oral Candidiasis in Dry Mouth Patients**

Treat risk factors for candidiasis if possible: manage dry mouth, evaluate systemic medications and modify if possible (e.g., discontinue steroid inhalers if other asthma management is possible; evaluate and manage diabetes); treat oral prostheses.

Fluconazole (Diflucan<sup>®</sup>) 100 mg tablets

Dispense: 8-15 tablets

Sig; Take 2 tablets on day 1 and then 1 tab per day for 6-13 days

Itraconazole (Sporanox<sup>®</sup>) solution 100 mg/10ml

Dispense: 140 ml – 280 ml

Sig: Swish and swallow 10 ml bid for 7 to 14 days

If Systemic Agents Cannot be Used – Recommended Topical Treatment Alternatives

Clotrimazole (Mycelex<sup>®</sup>) 10 mg troches

Disp: 70 troches

Sig: Dissolve one troche in the mouth five times per day for 14 days

Nystatin (Mycostatin<sup>®</sup>) 200 mg oral pastilles

Disp: 56 pastilles

Sig: Dissolve one pastille in the mouth four times per day for 14 days

**Xerostomia and Removable Prosthodontic Therapy**

Hyposalivation is often associated with reduced denture retention and generalized denture intolerance. It has long been recognized that the surface tension developed as a result of the layer of saliva interposed between the denture base and the supporting tissues is important for effective prosthesis retention. To achieve optimal surface tension between the denture (especially the maxillary) and the tissue, the intervening saliva must be thin and effectively wet the opposing surfaces. This allows the saliva to maximize contact between the surfaces, creating an adhesive force between saliva and the denture base. Maximum extension of the denture base within the physiologic limits of the supporting tissue and a bilaterally balanced occlusion are important for adequate denture retention

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in dry mouth patients. Denture adhesive may augment retention. A properly applied well-hydrated adhesive functions to enhance the surface tension between the denture and tissue. This replaces the otherwise saliva-deficient film layer thereby improving adhesion, eliminating voids between the denture and the mucosa, providing a cushioning or lubricating effect which helps to reduce mucosal irritation due to friction and prevents additional tissue dehydration. A properly applied adhesive will reduce food impaction between the denture and tissue, improve chewing efficiency and bite force, improve functional load distribution and facilitate the psychological well-being of the patient. For best results, these materials should be spread across the entire surface of the denture and firmly seated against the tissues.

Dry mouth denture wearers are also more prone to recurrent Candida infections. When the infection is confined to removable denture supporting tissues, treatment of the tissues can be effectively accomplished by placing an antifungal cream (e.g., nystatin or clotrimazole cream) or nystatin powder on the surface of the denture prior to placement. This should be done daily until the tissue appears clinically healthy and then for an additional two weeks. When the candidal infection involves other oral or pharyngeal soft tissues, a systemic agent may be considered. Additionally, the denture should be treated with one of the following protocols over the course of treatment.

### **Topical Treatment for Infected Dental Appliances**

Daily 30 minute soak in 0.12% chlorhexidine solution

Daily 30 minute soak in diluted sodium hypochlorite solution (10 ml or 2 teaspoons of 5.25% bleach, e.g., Clorox<sup>®</sup>, in 250 ml or 1 cup of water).

Decreased salivary output has a direct correlation with increased difficulty with denture function. Clinicians may consider implant-borne prostheses for dry mouth edentulous patients (Massad and Cagna).

## **BACTERIAL SIALADENITIS**

When salivary flow rates are diminished, secretions frequently become viscous and may block flow through the ductal system resulting in glandular swelling. This should be distinguished from swelling caused by an infection of the gland. A diminished flow rate may also result in retrograde bacterial infection of the duct system and the gland (bacterial sialadenitis). Swelling due to blockage may be relieved by glandular massage, whereas infection should be treated with antibiotics and, if possible, stimulation of salivary flow. Appropriate antibiotics are Penicillin VK<sup>®</sup> clindamycin or amoxicillin.

### **Antibiotic Treatment of Bacterial Sialadenitis**

Penicillin VK<sup>®</sup> 500 mg tablets

Dispense: 40 tablets

Sig: 2 tablets initially then 1 q 6 hrs for 10 days

Clindamycin 300 mg tablets

Dispense: 40 tablets

Sig: 2 initially then 1 q 6 hrs for 10 days

Amoxicillin 500 mg tablets

Dispense: 30 tablets

Sig: 2 tablets initially then 1 q 8 hrs for 10 days

NOTE ON PRODUCT TABLES: In the preparation of this manuscript, every effort has been taken to ensure the product information provided is accurate and up to date. However, the development, marketing and availability of products used in the management of xerostomia is constantly changing. Practitioners are advised to routinely check the literature, product suppliers and manufacturers.

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## **CHEMOTHERAPY**

### **INTRODUCTION**

Cancer chemotherapy is provided as a primary treatment for some cancers and as an adjunctive modality for other cancers. For example, leukemias are usually treated with chemotherapy alone. However, breast cancer may be treated with a combination of surgery, radiation, and chemotherapy. Certain head and neck tumors are treated with radiation and chemotherapy, because the combination appears to result in better response rates. The goal of chemotherapy is to eradicate the rapidly growing cells of the tumor. Unfortunately, chemotherapy is often toxic to other cells that rapidly divide normally. These include bone marrow, hair and the mucosa of the entire gastrointestinal tract, including the oral cavity.

#### ***Direct Cytotoxic Effect***

Chemotherapeutic agents affect the rapidly dividing cells of the target tumor and the lining epithelium, the oral ecology and the vascular, inflammatory and healing response of the oral cavity. These alterations may result in mucositis and ulceration of the oral mucosa.

#### ***Indirect Effects of Myelosuppression***

Chemotherapeutic agents also target the hemopoietic cells of the bone marrow, resulting in anemia, thrombocytopenia and leukopenia. This reduction in white cells heightens the risk of infection, primarily due to a decrease in the number of neutrophils (neutropenia = neutrophil count  $<2,000/\text{mm}^3$ ).

#### ***Infection***

Localized odontogenic infection may be difficult to diagnose in neutropenic patients since swelling is often not present. These infections will be more prone to spread to other body sites because of the loss of neutrophil activity. Between 25% and 54% of septicemia cases in neutropenic cancer patients may originate from oral infection. Infections in the oral cavity are associated with oral ulcers, periodontal disease, pulpal disease, pericoronal disease, and sinus infections. Infection can cause morbidity and death in patients receiving chemotherapy for treatment of acute leukemia. Fungal infections, particularly with *Candida* organisms, and viral infections, particularly with herpes simplex virus, are also increased in these patients.

#### ***Thrombocytopenia***

Decreased platelet number is a common complication in patients on chemotherapy. Patients are at risk for postoperative bleeding with dental surgery when the platelet count is below  $75,000/\text{mm}^3$ . Spontaneous mucosal bleeding can occur when the platelet count is below  $20,000/\text{mm}^3$ . The oncologist should be advised of the potential for bacteremia and/or bleeding associated with proposed dental procedures during chemotherapy.

### **MANAGEMENT**

#### ***Before Chemotherapy***

The optimum management for the patient receiving chemotherapy requires that the patient be seen by the dental practitioner before chemotherapy begins. In general, oral care should be completed at least one week before chemotherapy starts. This will leave approximately two weeks before the patient will be at greatest risk of oral complications. Coordination of oral care will require close consultation with the patient's medical oncologist.

***The medical oncologist should provide the dental professional with the following information:***

- The patient's current health history and the cancer diagnosis
- Palliative or curative therapy regimen
- Patient prognosis
- The anticipated number of chemotherapy treatment cycles and agents to be administered
- Route of administration (Patients with vascular access devices may require antibiotic premedication for dental treatment)
- Current laboratory values for the neutrophil count and the platelet count
- Anticipated timing of side-effects

The dental professional should provide the following information to the cancer treatment team:

- Dental treatment/management plan and timeline
- Unresolved oral health issues that may interrupt or complicate cancer treatment regime
- Unresolved oral health issues that may significantly effect patient comfort during therapy
- Anticipated oral complications

During the pre-treatment period, the following dental management issues should be addressed:

- Perform a thorough oral examination and obtain appropriate radiographs to establish baseline dental evaluation and identify pulpal, periapical, periodontal and/or pericoronary pathology that require immediate attention.
- Eliminate sources of intra-oral trauma (calculus, sharp teeth, ill-fitting prostheses/appliances, anything that could cause intra-oral trauma).
- Complete periodontal charting to establish baseline dental evaluation and identify periodontal problems that are likely to interrupt cancer treatment.
- Extract non-restorable teeth that could be sources of infection in the short term. This would include all teeth with severe periodontal disease, and those with gross decay that involves the pulp and are symptomatic. Time constraints prior to the beginning of chemotherapy may limit the role of endodontic therapy. If teeth have periapical radiolucencies and have been asymptomatic for the previous 90 days, they do not need to be managed before chemotherapy. In general, teeth with mild periodontal disease do not need to be managed before chemotherapy. If surgery is required, neutrophil count and platelet count will be critical. With neutrophil counts of  $> 2000/\text{mm}^3$  and platelet counts  $> 75,000/\text{mm}^3$ , no other interventions are necessary. However, if counts are lower supplementation may be needed. (See Table 1 for care during chemotherapy)
- Evaluate all partially erupted mandibular third molars. These should be extracted if at risk for pericoronitis.
- Perform oral prophylaxis with scaling.
- Restore advanced carious lesions and fractured restorations.
- Encourage patients not to wear removable appliances during chemotherapy, as this may serve as a source of local irritation. If they insist on wearing the appliance, it should be only for the minimum time necessary and the prosthesis must be kept clean.
- Remove orthodontic bands and appliances that may cause trauma to the oral mucosa.
- Encourage and reinforce that oral hygiene should continue after chemotherapy begins.

### ***During Chemotherapy***

As mentioned above, oral care is best provided before chemotherapy begins. However, sometimes care is needed after chemotherapy has been initiated. The chemotherapy cycle consists of cytotoxic drug administration followed by a rest period for healthy tissue recovery prior to repeated drug administration. An important clinical implication of this format is that peripheral white blood cell counts change dramatically during the course of this cycle. Appropriate timing of dental procedures during chemotherapy is critical. The risk of infection and septicemia is greatest when the patient's neutrophil count reaches their "nadir" (the lowest blood count). This occurs at approximately 10-14 days after chemotherapy is initiated. This is also the time that the platelet count will be low. If dental treatment is performed, it should be immediately preceded by consultation with the oncologist and documentation of the patient's hematological status. Treatment should be performed after the absolute neutrophil count (ANC) and platelet counts have recovered.

### ***Surgical procedures should be performed with the following in mind:***

- Absolute Neutrophil Count (ANC) should be equal to or greater than  $1,000/\text{mm}^3$
- Platelet count should be equal to or greater than  $75,000/\text{mm}^3$
- Clotting factors (PT, PTT, fibrinogen) should be normal
- Invasive dental procedures should be avoided if the ANC is expected to be less than  $1,000/\text{mm}^3$  within 10-14 days of the procedure

As with any guidelines, there are exceptions. Patients may not be seen for oral evaluation prior to beginning chemotherapy and develop an oral problem during treatment. In this case, their ANC may be far below  $1000/\text{mm}^3$  and their platelet count below  $75,000/\text{mm}^3$ . If such patients require surgical procedures, then they will need supportive measures to supplement this care. Table 13 lists supportive measures for invasive dental procedures.

## CHEMOTHERAPY

*Table 13 Supportive Measures for Chemotherapy Patients Undergoing Invasive Dental Procedures*

Lab Values	Recommendation	Comments
Neutrophils	Obtain from CBC or get from oncologist	
>2000/mm <sup>3</sup>	No prophylactic antibiotics	
1000-2000/mm <sup>3</sup>	AHA recommendations for prophylaxis with dental procedures	
<1000/mm <sup>3</sup>	IV Timentin 3.1 gm or Zosyn 3.375 gm 30 min before surgery and Amikacin 150 mg/m <sup>2</sup> 1 hour before surgery	
Platelets	Obtain from CBC platelet count or get from oncologist	
>75,000/mm <sup>3</sup>	No support needed	
40,000-70,000/mm <sup>3</sup>	Manage with local hemostasis measures including: pressure, topical thrombin, microfibrillar collagen, sutures, etc.	If not successful add platelet transfusions
<40,000/mm <sup>3</sup>	Transfuse platelets 1 hour before procedure. Goal is to raise count to 50,000/mm <sup>3</sup> . 1 unit of platelets will raise the count an average of 10,000/mm <sup>3</sup> .	Follow surgery with local hemostasis measures as listed above.

### **Oral Hygiene**

Patients should participate in the fullest oral hygiene protocol they can tolerate. This will decrease the severity of oral complications. Pain and/or edema of the oral cavity may prevent patients from continuing oral care during the peak of mucosal injury.

### **Brushing**

Continue brushing as per prior instructions. Use a soft toothbrush two to three times per day. Use a fluoride toothpaste as tolerated. Sponge brushes, if used, should be soaked in chlorhexidine. Rinsing with water or saline while brushing may help with plaque removal.

### **Flossing**

Use waxed or tape floss, which slides more easily and is less likely to damage soft tissue. It is important to make sure patients have the dexterity to floss, as the patient may damage tissue if too aggressive. Ongoing supervision of this intervention is particularly important during periods of myelosuppression.

### **Frequent Rinsing**

Frequent oral rinsing should be used in conjunction with, not in place of, an oral hygiene regime. Rinsing helps with the following:

- Cleans and lubricates tissues
- Prevents crusting
- Treats mucosal wounds
- Hydrates and irrigates mucosal tissues
- Soothes sore gingiva and mucosa
- Removes debris
- Prevents accumulation of debris and bacteria

Chlorhexidine has been proven to reduce plaque and oral organisms and may be used as an oral hygiene aid in patients undergoing chemotherapy. However it is not a replacement for the oral hygiene measures discussed above unless the patient cannot tolerate any of these. Due to alcohol content, burning may be a problem.

Table 14 Mouth Rinses

Mouth rinses	Composition/ Instructions for use:	Uses/Functions	Disadvantages
<b>Neutral Rinse</b>	1/4 tsp. Salt 1/4 tsp. baking soda 1 qt. H <sub>2</sub> O Use every 2 hours until soreness, nausea or ropy saliva contraindicate Switch to 1/2 tsp. soda and 1 qt. water or water only, if necessary Should not be swallowed	May be used during mucositis (omit salt) Neutralizes acids after emesis Dissolves thick, mucinous salivary secretions Soothing to irritated tissues Dislodges debris	None
<b>Saline Rinse</b>	1/2 tsp. salt 8 oz... water	Not damaging to oral mucosa Helps reduce mucosal irritation Increases moisture in mouth Removes thickened secretions and debris Recommended for treatment of leukemic gingivitis	None
<b>Calcium phosphate rinse (Caphasol®)</b>	Rinse 4x day or q 1 hr for mucositis	Remineralization	No published study on mucositis
<b>Chlorhexidine</b>	Rinse with 15-30 cc for 1 minute, 3 times per day Can be used as a mouthwash and gargle but should not be swallowed Allow 30 min before other oral hygiene procedures Rinsing with water intensifies unpleasant taste Should not replace dental evaluation/treatment An alcohol-free, aqueous 2% solution can be compounded by the pharmacist Can be applied locally with cotton swab	Used in presence of poor plaque control, signs of inflammation or decreased salivary flow Effective topical agent Has potent broad-spectrum antimicrobial activity Effective at low concentration Minimal absorption from the GI tract Results in fewer febrile days	May alter oral flora May delay healing Contains alcohol Stains teeth and restorations Toothpaste and nystatin reduce its effectiveness Promotes bacterial ( <i>pseudomonas</i> ) growth Unpleasant taste
<b>Hydrogen Peroxide</b>	Not recommended for use as a daily rinse Should be diluted 1:4 if used May be used to cleanse wounds, soften and loosen dried blood from lips and mouth Use for 1-2 day maximum Should be followed by therapeutic rinses	Helpful in periodontal infections when anaerobic microorganisms are involved	May delay wound healing Causes demineralization May promote emesis Causes dry mouth, thirst and discomfort Promotes fungal growth Unpleasant taste

### Maintenance of Prostheses

The patient should be encouraged not to wear their prosthesis while receiving chemotherapy. If patients must use their prosthesis, then it should be for as little as possible. They certainly should not wear their prosthesis at night or when they are having significant mouth soreness. The following procedures are recommended:

- Clean prosthesis twice a day with a soft brush and rinse well
- Soak prosthesis in antimicrobial solution for 30 minutes after cleaning (Sodium hypochlorite diluted 1:25 with water or chlorhexidine)

### **Mucositis**

Mucositis results from the direct cytotoxic effects of chemotherapeutic agents on the epithelial cells. The features of mucositis are described in the section on head and neck radiation.

### **General Guidelines**

- Mucositis is common when chemotherapy is given in high doses and repeating schedules, or when combined with radiation therapy. It is also more commonly seen when given to treat leukemia or GI cancer, or is used in conjunction with a bone marrow transplant
- Clinical oral mucositis typically begins 5-10 days following the initiation of chemotherapy and lasts 7-14 days.
- Overall, there appears to be a 10-15% risk of developing mucositis during the first cycle of cancer chemotherapy. Risk increases to about 70% during the second cycle if the patient experienced mucositis during the first cycle and medication dosage is not modified.
- Severity of chemotherapy-induced mucositis coincides with degree of neutropenia. Mucositis is typically most severe at the nadir (lowest value) of the neutrophil count.
- Mucositis is usually self-limiting and heals within 2-3 weeks. Resolution of mucositis correlates with recovery of white blood cells, specifically the neutrophils.
- The use of removable prosthetic appliances should be discontinued during periods of mucositis.
- Oral lesions should be evaluated for candidal organisms by Gram stain or KOH preparation when yeast infection is suspected or by viral culture if HSV infection is suspected.
- A variety of agents are recommended for the management of mucositis as a result of chemotherapy.

### **Mucositis-Associated Infections**

#### **Bacterial Infections**

Bacterial infections associated with mucositis can be difficult to diagnose because culture of mucositis lesions will often reveal flora that is present in the mouth, but not necessarily associated with mucositis. The early use of broad-spectrum antibiotics by the oncologist when patients develop a fever or become severely neutropenic has probably reduced the incidence of these infections in recent years. It should be remembered, however, that the ulceration of mucositis may provide an entry path for oral organisms into the bloodstream in myelosuppressed cancer patients. In recent years, gram-positive organisms found in the oral cavity have been more frequently identified as systemic infectious agents in patients on chemotherapy. It is important for the clinician to be aware of the potential for these infections, so that coordination of patient management can be achieved with the oncology team.

#### **Fungal Infections (Candida)**

Candidal infections of the oral mucosa are common in patients undergoing chemotherapy and can cause a burning or scalded sensation, distort taste and interfere with swallowing. However, in many patients no symptoms are reported until advanced stage of the infection, so thorough oral examination is imperative to detect these infections. Candidiasis is often easily treated if identified early. If not managed aggressively, oral infection has been shown to be a risk factor for spread to the esophagus or to the blood resulting in systemic dissemination. Systemic fungal infection is a common cause of infectious death in neutropenic patients because established systemic infections may be difficult to recognize and can prove difficult to treat.

Management of Candida infections may include the use of topical and/or systemic antifungal agents. Patients are often treated based on clinical presentation and laboratory confirmation while undergoing conventional chemotherapy, however prophylaxis with fluconazole has become a standard of care in most bone marrow/peripheral stem cell transplant centers. Multiple studies have demonstrated that nystatin prophylaxis in the immunocompromised host is no better than placebo. The dental health care provider is in the unique position to advise oncologists as to the appropriate selection of antifungal agents preventing possible unnecessary use. Procedures to manage Candida infections are summarized below:

- Perform culture, gram stain or potassium hydroxide (KOH) wet prep to assist diagnosis of candidiasis.
- Treat infections aggressively.
- If accompanied by sore throat, evaluate for esophageal candidiasis.
- Fluconazole tablets or clotrimazole troches are the most commonly used medications.
- Itraconazole suspension may be used if patient has resistance to fluconazole.
- Generally avoid nystatin suspension due to sugar content, limited contact time and poor patient acceptance.
- Nystatin pastilles are an option.

### **Viral infections**

Herpes simplex virus type 1 (HSV-1) reactivation has serious local implications during chemotherapy due to pain, impaired hydration and nutrition. It most commonly occurs in conjunction with chemotherapy mucositis, resulting in multiple ulcerations involving any intraoral and perioral soft tissue surfaces. Since these patients are expected to develop mucositis secondary to their chemotherapy, HSV reactivation may be overlooked as an etiologic factor in oral ulcerations. Mucositis complicated by HSV reactivation tends to be more severe and last longer. In leukemia and bone marrow transplant patients, reactivation of HSV occurs in 50-80% of HSV seropositive patients. Prophylactic acyclovir offers effective control and is commonly used in bone marrow transplant patients. However, it is not routinely used in patients on cancer chemotherapy. These patients should be evaluated closely for HSV reactivation. The systemic consequence of HSV infection is the disruption of the mucosal barrier, allowing a portal of entry for commensal oral microorganisms, which can lead to sepsis. Although much less common than HSV, herpes varicella zoster virus (VZV) cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesviruses (HHV-6, 7, 8) as well as community respiratory viruses have also proven to be problematic during the course of chemotherapy.

Procedures to manage viral infections are summarized below:

- All lip, palate, gingiva and dorsal tongue lesions in HSV-antibody positive patients should be cultured for HSV unless the patient is already taking or has been prophylaxed with acyclovir (Zovirax<sup>®</sup>).
- Ointments containing acyclovir antivirals are probably not appropriate for these patients as extent of disease requires systemic therapy.
- Outpatient treatment for less severe disease: acyclovir capsules
- Inpatient treatment in patients with severe disease: acyclovir IV
- Other options with advantage of better patient compliance but higher cost: famciclovir (Famvir<sup>®</sup>) valacyclovir (Valtrex<sup>®</sup>)
- For acyclovir-resistant viruses; Foscarnet (Foscavir<sup>®</sup>)
- Cytomegalovirus (CMV) infection is not uncommon in immunosuppressed (transplant) patients and is best managed with systemic gancyclovir.

**Table 15 Medications for HSV Infection Associated with Chemotherapy Mucositis**

Acyclovir (Zovirax <sup>®</sup> ) 400 mg capsules Disp: 21 capsules Sig: Take one tablet three times per day for seven days
Acyclovir (Zovirax <sup>®</sup> ) IV Sig: 5mg/kg every eight hours for seven days
Famciclovir (Famvir <sup>®</sup> ) 500 mg capsules Disp: 14 capsules Sig: Take one capsule two times per day for seven days
Valacyclovir (Valtrex <sup>®</sup> ) 500 mg capsules Disp: 14 capsules Sig: Take one capsule two times per day for seven days

Xerostomia may occur in association with chemotherapy, although it is typically caused by anticholinergic medication utilized to control nausea and emesis. The symptom is usually transient in nature and often resolves completely following treatment. Patients may complain of dryness, a change in the consistency of their saliva and difficulty in swallowing. Challenges in eating can be addressed by instructing patients to take small bites, chew slowly and sip liquids frequently.

Abnormal taste (dysgeusia) can also occur as a side-effect of cancer chemotherapy. Patients may complain of no taste or that foods do not taste as they did prior to chemotherapy. Unpleasant tastes are often due to the spread of medications within the oral cavity. Dysgeusia may further reduce the patient's appetite contributing to poor oral intake, requiring parenteral nutrition. These changes are generally transient in nature and subside following treatment.

### **Neurotoxicity**

Chemotherapeutic agents may have a toxic effect on peripheral, autonomic and cranial nerves. Drug-induced neurologic disorders may induce a persistent, deep pain that mimics that of dental or periodontal origin. If this occurs, reassure the patient and administer palliative treatment to minimize discomfort. These neurological effects usually subside when the course of chemotherapy has been completed.

### **Growth Factors**

Growth factors are a promising area of study for relief and recovery of mucositis including colony stimulating factors (GCSF and GMCSF), transforming growth factor beta (TGFb), and keratinocyte growth factor (KGF) among others. Palifermin, a modification of keratinocyte growth factor, is the only FDA-approved systemic drug for the treatment or prevention of mucositis, and only for patients receiving autologous hematopoietic stem cell transplant. It is used to reduce the chance of developing severe mucositis and to shorten the time with severe mucositis in patients receiving treatment for certain types of cancer. Palifermin is believed to work through a series of complex interactions, resulting in the stimulation of cells of the lining of the oral mucosa leading to faster replacement of the cells damaged by chemotherapy and radiation. It is administered intravenously for three days prior to treatment and three days following treatment.

### **Biohazard Handling Of Body Secretions During Chemotherapy**

The healthcare provider should be aware that the vomitus, tears and saliva of a patient undergoing chemotherapy contain cytotoxic drugs and should be handled as hazardous waste.

#### After Chemotherapy

Before next course of therapy:

- Emphasize self-care
- Place on 3 month recall
- Call oncologist to determine adequate hematologic status for dental therapy

After completion of chemotherapy:

- Maintain normal dental recall schedule
- Confirm normal hematologic status
- Maintain optimal oral health in the event further myelosuppressive therapy is required

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**BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW (BRONJ)**

Bisphosphonates (BPs) are now used extensively to manage a variety of bone-related conditions such as osteoporosis, Paget's disease, osteogenesis imperfecta and the skeletal-related events (SREs) associated with malignancy. SREs such as pathologic fracture, hypercalcemia of malignancy, spinal cord compression or bone pain requiring palliative radiation or surgery negatively impact the cancer patient's quality of life. The cancers most frequently associated with SREs are: multiple myeloma, breast cancer, prostate cancer, thyroid cancer, lung cancer and bladder cancer.

In the oncology setting, BPs are typically administered intravenously. Approximately one-half the dose is taken up by bone. The residual is excreted by the kidneys. BPs preferentially bind to and become incorporated into the osseous tissues, especially those with high turnover rates. When the bone in which they are deposited undergoes resorption, they are released and taken up by the osteoclast. Thus, the long half-lives attributed to BPs, which in some cases exceeds 10 years, are primarily determined by the rate of skeletal remodeling.

**MECHANISM OF ACTION**

Bisphosphonates are a unique class of drugs characterized pharmacologically by their affinity for bone and ability to inhibit bone resorption. The mechanisms by which BPs inhibit bone resorption are not fully understood. BPs not only inhibit hydroxyapatite dissolution, but also act through a multitude of pathways to alter the overall osteoblast/osteoclast balance. First generation agents are metabolized by the osteoclast into non-hydrolyzable cytotoxic ATP analogs, which induce apoptosis. In contrast, newer BPs such as the nitrogen-containing agents pamidronate and zoledronic acid are not metabolized by the osteoclast, but act through several different mechanisms. These newer agents inhibit the mevalonate pathway of lipid biosynthesis leading to reduced production of two isoprenoid lipid intermediates: farnesyl diphosphate (FPP) and geranylgeranyl diphosphate. FPP synthase is required for the prenylation of small signaling proteins such as Ras, Rho, and Rac. These proteins regulate a variety of cellular processes such as cell morphology, integrin signaling, membrane ruffling, endosome transport and apoptosis.

**BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW (BRONJ)**

The association between jaw osteonecrosis and exposure to BPs was first reported in 2003. The author described 36 patients who experienced painful bone exposures affecting the mandible, maxilla or both. All patients had been exposed to or were currently taking pamidronate, zoledronic acid or both, and all but one were prescribed BPs as part of cancer treatment. Subsequently, numerous other case reports have been published. Specific criteria to confirm a case of BRONJ are: the presence of exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks affecting a patient who is either on or has been previously exposed to a BP and who has no history of irradiation therapy to the jaws. A suspected case meets the aforementioned criteria, except it has not been present for greater than 8 weeks. There is an International Classification of Diseases, Ninth Revision code applicable to BRONJ (ICD-9-CM 733.45, "aseptic necrosis jaw").

The true incidence of BRONJ is unknown and risk estimates should be interpreted with caution. For oncology-related cases, the incidence is estimated to be 4% - 13%, with a median onset of between 22 and 39 months. In a review of 626 reported cases of BRONJ, the authors determined that 92.7% of the cases were associated with exposure to zoledronic acid (42.6%), pamidronate (26.9%) or both (23.2%). Worldwide, the number of patients exposed to these most frequently implicated drugs is estimated to be 2.5 million. The universal acceptance and use of the refined diagnostic definition for BRONJ, along with its newly available ICD-9 code, should result in more accurate epidemiologic assessments in the future.

***Etiopathogenesis***

A causal relationship between BPs and BRONJ has not been clearly established. Furthermore the therapeutic actions of BPs are still under investigation. The strong association of BP exposure and BRONJ in the oncology cohort is compelling. The predominant contemporary theory for BRONJ postulates that BP-induced uncoupling of the functional osteoclast/osteoblast balance leads to impaired bone remodeling, which in turn affects the ability of the bone to respond to normal physiologic and inflammatory burdens. Others propose the antiangiogenic or soft tissue toxicity properties of BPs contribute to the development of BRONJ. Such putative mechanisms of pathogenesis need not be mutually exclusive, and the development of BRONJ likely results from the convergence of a multitude of events.

One of the more perplexing aspects of BRONJ is its proclivity for affecting only the jaws. Some considerations unique to the jaws may help explain this feature. The thin mucosal tissues of the oral cavity are easily breached through physiologic or traumatic events and periodontal or pulpal inflammation frequently extends into the surrounding bone. As a consequence, the osseous tissues may be exposed to the contaminated milieu of the oral cavity. Secondly, the bone turnover rate of the jaws, particularly the alveolar processes, is higher than most other bones in the body. Thus, it is likely that administered BP is preferentially concentrated in the alveolar bone.

### ***Risk factors***

In assessing more than 600 reported cases of BRONJ, several factors have been identified and/or purported to increase the risk of BRONJ. Of these, the concept of drug potency and dose accumulation appear most important. The vast majority of reported BRONJ cases have been associated with prolonged intravenous dosing of the most powerful nitrogen-containing BPs, especially zoledronic acid and, to lesser extent, pamidronate. This scenario is the typically observed in the oncology setting, where the most powerful BPs are often prescribed as palliative therapy to reduce the SREs of malignancy. The estimated mean time to onset of BRONJ with zoledronic acid and pamidronate exposure is 18 months and 39-72 months, respectively.

An antecedent traumatic insult, most typically from dentoalveolar surgery, is observed in approximately 60% of cases of BRONJ. Trauma related to ill-fitting dentures or normal physiologic trauma to the relatively delicate lingual plate or bony prominences of tori and exostoses has also been observed. As most surgical procedures are most likely performed to address oral infection, there is concern that oral infection contributes to BRONJ. However, as available evidence is largely limited to retrospective studies, it is difficult to determine if infection preceded BRONJ, or merely developed in response.

Other predisposing factors for the development of BRONJ include: female gender, advanced age, chemotherapy (e.g., thalidomide, bortezomib), jawbone irradiation, glucocorticoid therapy, alcohol use, tobacco use, poor nutrition, and co-morbidities such as anemia, diabetes mellitus, peripheral vascular disease and obesity. The evidence for these factors is less conclusive. While further studies are indicated to determine the relevance of all of these parameters, it appears clear the oncology patient with co-morbid disease undergoing prolonged treatment with a potent BP is at highest risk.

### ***Clinical presentation and diagnosis***

The essential clinical feature of BRONJ is an area of exposed necrotic bone, varying in size from a few millimeters to several centimeters. The mandible is more frequently involved than the maxilla (2-3:1) and areas of bony prominence are at particular risk. Lesions may be solitary or multiple, unilateral or bilateral. Pain is present in about 60% of cases. Overt infection may or may not be present. Other conditions to consider in the differential diagnosis include: periodontal disease, gingivitis, mucositis, infectious osteomyelitis, sinusitis, odontogenic infection, temporomandibular joint disease, osteoradionecrosis, neuralgia-inducing cavitation osteonecrosis and primary or metastatic tumors.

Radiographic findings of BRONJ are not specific and typically not appreciable until 30% to 50% of demineralization has occurred. Early lesions may exhibit no radiographic changes or only slight hints of lucencies and/or radiopacities. More advanced cases may reveal radiographic areas of moth-eaten, poorly-defined lucencies and radiopaque sequestra. The appearance may mimic periapical pathosis, osteomyelitis or a primary or metastatic tumor. A strong suspicion of metastatic disease mandates a biopsy. Otherwise, a biopsy is generally not recommended for fear of aggravating BRONJ. More advanced imaging techniques (e.g., CT, MRI) may help to delineate the extent of necrosis.

Histologic assessment of biopsy specimens are non-specific and reveal necrotic bone, granulation tissue and bacterial debris. The contaminated milieu of the oral cavity renders routine microbiologic culturing problematic. However, culture results from properly attained samples may help refine antimicrobial therapy.

In an effort to direct rational therapeutic protocols and assess their impact on therapy, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has recommended a staging system for BRONJ (Table 16). Some contend that this system is too simplistic and should be modified to include lesion size along with information derived from dental radiographs, CT, MRI and biopsy.

## BISPHOSPHONATE-RELATED OSTEONECROSIS

*Table 16 Staging*

Category	Features
At Risk	No apparent exposed/necrotic bone in patients who have been treated with either oral or IV BPs.
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent damage.
Stage 3	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: Pathologic fracture Extraoral fistula Osteolysis extending to the inferior border.

### MANAGEMENT

BRONJ appears to be recalcitrant to currently available therapies. Current therapeutic recommendations are limited to a consensus of expert opinions. The therapeutic aims are to eliminate pain, control infection and minimize further disease progression. In virtually all cases, a conservative and deliberate approach is recommended.

*Table 17 Recommended Therapies*

Stage	Recommendations
Stage 1	Frequent monitoring (every 2-3 months) Daily use of an oral antimicrobial rinse such as chlorhexidine 0.12% Instructions to perform meticulous home care. Dental care to control disease; invasive procedures should generally be avoided. Loose bony sequestra should be carefully removed without exposing underlying uninvolved bone. Symptomatic teeth within exposed necrotic bone may be carefully extracted, as this action is unlikely to exacerbate the established necrotic process.
Stage 2	Stage 1 recommendations, plus systemic antimicrobial therapy and pain control. Acceptable choices include oral penicillin, quinolones, metronidazole, clindamycin, doxycycline, and erythromycin. Culture and sensitivity testing is recommended to guide therapy.
Stage 3	Surgical debridement/resection with antimicrobial therapy may offer long-term palliation.

The role of surgery in the management of BRONJ remains a topic of ongoing debate. Since BP's are incorporated into the entire skeleton, it is difficult to determine the extent of affected bone when undertaking a surgical approach. Current recommendations allow for meticulous debridement and sequestrectomy. Aggressive surgery is deemed a treatment of "last resort" to manage only the most severe cases.

The issue of discontinuing BP therapy remains unresolved. On principle, some propose that oncology-based BP therapy may be discontinued after two years, provided the patient is experiencing remission or is in a stable state. However, others recommend BPs be administered for as long as the patient can tolerate the therapy. While there is no conclusive evidence that discontinuing BP therapy leads to resolution of BRONJ, the AAOMS contends that discontinuation may be valuable in stabilizing existing sites of BRONJ and reducing clinical symptoms. In contrast, many physicians question the wisdom of discontinuing these drugs, given the totality of their overall benefit.

A variety of other adjunctive therapies to manage BRONJ such as hyperbaric oxygen, ozone therapy, laser therapy, tetracycline-guided debridement and parathyroid hormone supplementation have been proposed. However, further study is necessary to develop specific recommendations.

### Prevention

Given the limitations noted above regarding BRONJ therapy, the primary focus must be to reduce the risk of BRONJ occurring in at-risk patients. It is generally accepted that by optimizing the patient's oral health prior to their undergoing BP therapy, the risk of BRONJ may be reduced. The overall approach is similar to that recommended to reduce the risk of osteoradionecrosis occurring in the patient scheduled to undergo head and neck irradiation. Prior to initiating BP therapy the benefits of therapy, along with the risks and signs and symptoms of BRONJ, should be discussed in a balanced manner and an informed consent should be obtained.

The patient should also undergo a comprehensive dental assessment and obtain all necessary treatment required to control active dental disease. Whenever possible, teeth that are unsalvageable or not maintainable should be extracted, periodontal health should be optimized and all restorative care should be accomplished prior to initiating BP therapy. The patient should be educated on the importance of maintaining meticulous oral hygiene and the importance of promptly reporting any pain, swelling or exposed bone to their provider.

Once BP therapy is initiated, the focus on maintaining oral health remains paramount. The patient should undergo frequent recall assessment, meticulous oral hygiene should be reinforced and necessary restorative care should be accomplished. However, therapies that violate the mucosal or osseous tissues (e.g., periodontal surgery, implant placement, extractions, etc.) should be avoided. Non-restorable teeth should be managed with endodontic therapy and intentional root amputation. Some have proposed using orthodontic elastics to gradually and atraumatically extract non-restorable teeth.

### **SUMMARY**

While much remains to be learned about BRONJ, it appears to represent a classic example of an unintended consequence of a desired therapeutic effect. Ongoing refinement of BP dosing regimens to address SREs of malignancy may lead to a reduction in the cumulative dose administered to the patient. The development of newer osteoprotective drugs such as denosumab, which do not accumulate in bone, may lead to the availability of safer alternatives. Finally, research to identify potential predictive markers of BRONJ (e.g., biologic, radiologic, genetic) may lead to the development of earlier and more predictable interventional therapies.

Today, current therapeutic strategies to manage BRONJ emphasize prevention and are largely limited to conservative measures for established cases. In the oncology cohort, for whom the risk of BRONJ is clearly greatest, the benefit of BP-induced osteoprotection appears to outweigh the risk.

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## HEMATOPOIETIC STEM CELL TRANSPLANT

### INTRODUCTION

With hematopoietic stem cell transplant (HSCT), the bone marrow is intentionally destroyed by intensive-dose chemotherapy, with or without radiation therapy. The goals of HSCT can be multi-fold and include a) elimination of underlying malignant disease and establishment of a normal functional marrow / immune system, or b) establishment of a healthy functional immune system when there is underlying immune deficiency/dysfunction disease. Prior to infusion of stem cells patients are treated (conditioned) with very high doses of chemotherapy or chemoradiotherapy. These conditioning regimens are typically sufficient to destroy the patient's bone marrow, essentially leaving them with no functioning immune system. The patient is then transplanted with hematopoietic stem cells, which repopulate their bone marrow, thus establishing a new functional marrow and immune system. Affected bone marrow may be replaced with stem cells from either the patient or a donor. In some cases, transplantation is used to replace bone marrow that is either diseased or defective. Alternatively, it may be given as a treatment for cancer, necessitating rescue after high-dose chemotherapy that would potentially be lethal. Diseases typically treated with HSCT transplant are leukemias, aplastic anemia, myelodysplasia, myeloma, lymphoma, certain solid tumors and inborn or acquired immune disorders (e.g., severe combined immunodeficiency). Intensive conditioning regimens given for HSCT are associated with numerous and often severe oral complications.

### TYPES OF DONORS FOR HSCT

#### *Autologous transplant*

The patient's own bone marrow and/or peripheral blood stem cells are removed and preserved. The patient is given high dose chemotherapy and then transplanted with their own cells. Associated oral complications include those related to chemotherapy and neutropenia. Overall transplant-related mortality rate is approximately 2%.

#### *Allogeneic transplant*

Bone marrow, peripheral blood stem cells or umbilical cord cells are collected from a HLA (Human leukocyte antigen)-matched individual who can be related or unrelated to the patient. If a HLA-matched donor is not available, 1 or, at times, a 2-antigen mismatched donor can be considered. Associated oral complications include those from conditioning regimens, myeloablation and graft-versus-host disease (GVHD). Overall transplant-related mortality rate is approximately 25% in related individuals and 40-60% with an unrelated donor.

#### *Syngeneic transplant*

Hematopoietic stem cells are taken from an identical twin. Associated oral complications are similar to those encountered with autologous transplant and are generally related to conditioning regimen toxicities and related myeloablation. Syngeneic GVHD and opportunistic infections occur less frequently than with allogeneic transplants. Overall transplant-related mortality rate is approximately 2%.

### MANAGEMENT

#### *Before and During Transplant*

Oral hygiene and dental recommendations should be related to the prescribed conditioning therapy and coordinated with the transplant physician. Immediacy and extent of treatment should be determined by consultation between dentist and transplant physician as dictated by the state of the disease, immunocompetency, goals and expected outcome of therapy. Most oral complications are comparable to those with chemotherapy; management would be the same as described previously. It may be more likely for these patients to be neutropenic and thrombocytopenic prior to transplant than those receiving chemotherapy as sole treatment, due to recent standard therapy for the patient's underlying disease. Therefore the need for prophylactic antibiotics and platelet transfusions with invasive dental treatment may be more common.

#### *Infection Prophylaxis*

Reactivation of viruses from the herpes group in HSCT patients can lead to severe illness and is associated with an increase in morbidity and mortality. Patients undergo testing for prior exposure to herpes simplex virus, cytomegalovirus, varicella-zoster virus and, to a lesser extent, Epstein-Barr virus in advance of transplantation. The standard prophylaxis against reactivation of herpes simplex virus is acyclovir capsules (200 mg t.i.d.) or by infusion (250 mg/m<sup>2</sup> q8h). Acyclovir is usually initiated between the start of conditioning therapy and day 1 after transplantation, and is often continued until patients are immunocompetent following HSCT

recovery. Medications considered for prophylaxis against CMV include ganciclovir, foscarnet and cidofovir with ganciclovir being the most commonly used; additionally, strategies to prevent exposure to CMV are utilized that include administration of CMV-negative blood products and prevention of exposure to CMV infected individuals.

Many centers employ systemic antifungal prophylaxis to prevent or lessen the risk for fungal infections following HSCT. Typical therapy is oral fluconazole 400 mg per day beginning with conditioning for transplant and continuing through neutropenia. Infusion with a similar dose may be used with compromised oral intake. Alternatives to fluconazole include itraconazole, voriconazole, posaconazole and amphotericin B.

Prophylactic antibiotics are also commonly used during periods of profound neutropenia with protocols being quite variable. Prophylaxis for encapsulated bacteria with agents such as Bactrim is used for extended periods of time post transplant.

### **Acute Graft vs Host Disease**

Patients who receive allogeneic HSCT transplants are at risk for graft versus host disease (GVHD). The transplanted immunocompetent donor cells (the graft) recognize the patient's tissues (the host) as being "foreign" and direct immune-based attack against host tissues. GVHD can occur in an acute version and a chronic version. Acute GVHD can manifest early in the post transplant period up until day 120 post-transplant. Orally, it manifests primarily as mucosal atrophy and erythema with possible lichenoid hyperkeratotic striae and plaques. In the first 21 days post-transplant, oral acute GVHD can be difficult to distinguish from conditioning regimen-related mucositis. Symptomatic oral acute GVHD can be managed utilizing topical steroids and other topical immunosuppressants.

### **After Transplant**

In the post-transplant period, oral care should be maintained. During the first 100 days after transplant the patient is at increased risk of multiple complications. The risk for complications gradually decreases after day 100 as marrow function increases and immunity is restored over the next 6 to 12 months. The following recommendations are a guide for post-transplant oral care:

- Up to 100 days post-transplant – routine oral hygiene, emergency dental treatment only and supportive oral care as needed
- From 100 days to 365 days post-transplant – emergency dental care, oral hygiene and xerostomia management
- After 180 days for autologous transplant patients and after 365 days post-transplant for allogeneic transplant patients routine oral hygiene, standard dental care unless chronic GVHD
- If chronic GVHD - emergency care only
- Prophylactic antibiotics and other supportive care should be given to patients for emergency/urgent dental care.

### **Chronic Graft vs Host Disease**

The onset of chronic GVHD occurs between approximately 70 and 500 days after transplantation in 33-44% of allogeneic BMT/ HSCT transplant recipients. Chronic GVHD can progress from acute GVHD (progressive disease), occur without prior acute GVHD (de novo disease), or after resolution of acute GVHD (quiescent disease). In chronic GVHD, the host (patient) possesses iso-antigens which are perceived as foreign to the grafted immune system, thereby stimulating the immunocompetent grafted lymphoid cells to react against the host. Chronic GVHD primarily affects the skin, liver, eyes and mouth. Oral manifestations occur in 90% of patients with evidence of GVHD in other organs, although the mouth can occasionally be the only site of activity. Oral manifestations include epithelial atrophy, erythema, ulcerative lesions, lichenoid hyperkeratotic lesions, and xerostomia/salivary gland hypofunction. Oral pain is a common presenting symptom of these manifestations. Occasionally, taste dysfunction is associated with chronic GVHD. Appropriate history and diagnostic testing differentiate the lesions of GVHD from other oral diseases with similar clinical presentation. The patients during this stage are at risk for oral infections and xerostomia following GVHD and should continue with oral care protocols twice a day.

The diagnosis of chronic GVHD is based on clinical presentation, evidence of systemic GVHD, and, when necessary, positive labial salivary gland/oral mucosal biopsy. The oncologist may request a consulting dentist to perform this procedure. It is important to discuss this with the pathologist who will read the biopsy specimen, so that an appropriate amount and type of tissue is submitted. Both mucosal epithelium from clinically involved areas, plus underlying minor salivary glands should be obtained. Patients with active chronic GVHD will remain at risk for the oral opportunistic infections due to the underlying GVHD and the immunosuppressive therapy used to manage GVHD. Therefore candidal and herpes virus infections are common. As a result, both viral and fungal prophylaxis are often continued. Systemic manifestations of chronic GVHD are typically managed with steroid and other immunosuppressive drugs. It is not uncommon for oral lesions to remain when all other manifestations have been managed systemically. The oncologist may request that the dentist manage the remaining oral lesions. Generally, asymptomatic non-ulcerated (non-pseudomembranous)

oral GVHD does not require therapy. Topical therapy for oral GVHD is most effective for managing the symptoms of oral GVHD. Therapies include topical steroids, azathioprine, tacrolimus and psoralen with ultraviolet A light therapy (PUVA). (Table 18)

Chronic GVHD often affects the salivary glands, resulting in Sjögren's Syndrome-like symptoms including both xerostomia and xerophthalmia. Severe GVHD can eventually result in permanent damage to the glands due to acinar atrophy and fibrosis. This can leave the patient severely xerostomic and increases their risk for rampant decay. See the Management of Xerostomia section.

**Drug-Induced Gingival Overgrowth**

Bone marrow transplant patients with GVHD will commonly take cyclosporine for immunosuppressant therapy. High and persistent dosing with this medication is associated with gingival overgrowth. In severe cases, gingival overgrowth may require periodontal surgery. Re-growth is common and repeated therapy is often indicated. Dental health care providers may consult with the oncologist regarding the use of alternative immunosuppressants.

**Secondary Malignancies**

Cancer therapies and chronic immunosuppressant therapy increase the risk for subsequent malignancies in the HSCT patient. This is particularly true for the skin and mucosa. It is imperative that frequent head and neck cancer screens be performed in these patients.

*Table 18 Therapies for Intra-oral Chronic GVHD*

<p>Rx: Dexamethasone oral elixir (0.1 mg/ml)                  Disp: 16 oz..                  Sig: 1 tsp. swished and held in mouth for 4-5 minutes, spit out. Use 3-6 times a day depending on severity of oral lesions.</p>
<p>Rx: Clobetasol cream or gel (0.015 %)                  Disp: One tube                  Sig: Apply carefully to pseudomembranous ulcerations twice a day until resolved. (Consideration can then be given to continued treating with dexamethasone oral rinses).</p>
<p>Rx: Lotrizon Cream (Betamethasone/Clotrimazole)                  Disp: 15 gm tube                  Sig: Apply to intraoral lesions three times per day. Patient must allow cream to remain in place as long as possible with application. (Therefore this must be done when patient can give this their total attention.)</p>
<p>Rx: Azathioprine oral rinse (8 mg/ml)                  Disp: Compounded from tables with bland flavored base. Disp 16 oz...                  Sig: 5-10 ml swished/held for 4-5 minutes, spit out, every 4-8 hours</p>
<p>Rx: PUVA therapy                  Disp: Psoralen 10 mg tablets                  Sig: Take 20 mg one hour before appointment.                  Begin ultraviolet A therapy at 0.5 J/cm<sup>2</sup> and increase by 0.5 J/cm<sup>2</sup> with each appointment. Dose must be tailored to patient based on response. Warn patient that for 24 hours they must protect themselves from sun exposure. Ultraviolet A light can be provided by using a NUVA light. These should be tested to determine output so dose can be predicted. They should be placed approximately 1cm from the tissue to be treated.</p>

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## MANAGEMENT OF OROPHARYNGEAL MUCOSITIS PAIN

### INTRODUCTION

One of the central fears of all cancer patients is pain – both pain caused by cancer and pain arising from cancer therapy. Patients can present with tumor pain involving various sites of the body, including the head and neck and oropharynx, treatment-related pain, and pre-existing pain complaints such as low back pain or other chronic pain problems. All these are intertwined in the patient's ongoing pain experience, and must be addressed if the patient's pain is to be successfully managed.

While significant advances continue to be made in the field of supportive care for cancer, oropharyngeal mucositis (OPM) continues to be a frequent and debilitating oral side effect of aggressive cancer therapies. However, mucositis is much more than just mouth and throat pain. Chemotherapy and radiation can cause significant mucosal damage but can also have a marked effect on oral function and the patient's psychological well-being. From a patient's perspective, the pain and disability from oral mucositis can be all consuming, and represent the worst experience that the patient remembers from their cancer treatment. Studies have shown that the mucositis associated with myeloablative treatments for hematopoietic stem cell transplant can be the most frequently reported cause of pain and is rated as the most debilitating side effect and, in fact, as the worst transplant-related experience by patients. Severe OPM significantly affects the cancer patient's psychological state, producing mood disturbances, specifically increased depression and anger.

The impact of mucositis on the patient's physical and psychological well-being is pervasive and profound, since mucositis and the pain it causes can:

- Interfere with therapy by necessitating treatment delays and dose reductions that can interfere with cancer cures.
- Increase risk of other complications including infections and bleeding
- Increase the cost of care
- Interfere with oral function, making it difficult or impossible to eat, swallow or drink
- Affect mood and behavior
- Dramatically diminish quality of life

Advancements in the field of supportive care relative to the prevention and management of OPM continue to be made. Evidence-based guidelines, such as those produced by the Multinational Association of Supportive Care in Cancer (MASCC), have identified mucositis prevention and treatment strategies that can be beneficial for patient care based on level II and III evidence. Unfortunately, only a relatively small number of treatments met criteria for inclusion in the guidelines. Examples of effective treatments include the use of palifermin (a mucosal growth factor) that has been shown to be able to significantly reduce the frequency and severity of OPM in patients undergoing autologous hematopoietic cell transplants (HCT) and oral cryotherapy (so called "ice chip therapy") that has been shown to reduce the frequency and severity of oral mucositis in patients treated with high dose 5-FU, melphalan, and edatrexate. But these treatments, while effective for specific cancer therapy protocols, cannot be used with all patients at risk for OPM, leaving significant numbers of patients to potentially suffer. Considerably more research is clearly needed. In most instances, current strategies focus on palliation of pain symptoms until the oral tissues involved can recover and heal.

Currently, management of mucositis pain continues to rely on a multidimensional approach to pain and symptom management. Evidence-based guidelines suffer from the lack of sufficient evidence to manage OPM across the scope of cancer patients and there still is a need for an organized and cogent approach to oral mucositis pain management that allows a comprehensive approach to patient care in the face of major gaps in scientific evidence. The oral mucositis management guidelines recently published by the National Cancer Care Network (NCCN) represent an attempt to utilize a reasonable combination of levels of evidence that combines "evidence-based guidelines" with lesser levels of evidence in a manner that allows for more comprehensive mucositis management where gaps in evidence occur.

One major clinical cause of ineffective mucositis pain management is simply under-treatment. In general, the under-treatment of cancer and cancer therapy-related pain is a recognized problem throughout oncology, for a number of reasons. Clinician-related factors in the under-treatment of pain can include inadequate knowledge of pain management, poor assessment of pain, and concerns about prescribing controlled substances, especially opioids with the potential for patient tolerance, addiction and side effects. Patient-related factors include reluctance to report pain, fear that pain means the primary treatment is failing, concern about being perceived as a "complainer", reluctance to take pain medications, fear of addiction/dependence and concerns about side-effects.

## MANAGEMENT OF ORAL MUCOSITIS PAIN

Factors such as gender, culture, education, occupation, economic status and experience with medical care systems also contribute to differences in response to treatment and the incidence of side effects. All of these factors must be considered, not only for the treatment of pain, but also in the approach of medicine and care of patients from diverse cultural and educational backgrounds. Delivery of individually appropriate pain control requires more than knowledge of pathobiology and pharmacology, and must extend to an understanding of cultural and ethnic values, linguistic influences on pain expression and description of pain quality, patients' reaction to the pain experience (seeking healthcare), coping styles and adopting disability status, the patient/provider relationship and finally, the patient's receptivity to treatment and compliance.

### PAIN MANAGEMENT FOR MUCOSITIS: GENERAL PRINCIPLES

OPM pain can be generally classified as an acute cancer treatment-related pain although it clearly has several unique qualities and the management of oral mucositis pain can generally follow the basic principles used for acute pain management. OPM pain results from direct local injury to tissues and inflammation that activates nociceptive receptors at the site of injury. The pain lasts for a relatively limited time, as short as 1-2 weeks for chemotherapy-related mucositis and usually less than 3 months for head and neck radiation-induced mucositis. Mucositis pain will usually resolve once the underlying mucosal tissue damage resolves. A possible exception is mucositis resulting from radiotherapy, which may produce chronic pain. For effective management of mucositis pain, a multidimensional approach to patient care, with a supporting pain management framework and mucositis pain management guidelines is required for more comprehensive management, increased success, and patient comfort.

The basic tenets of a standard acute pain management model are as follows:

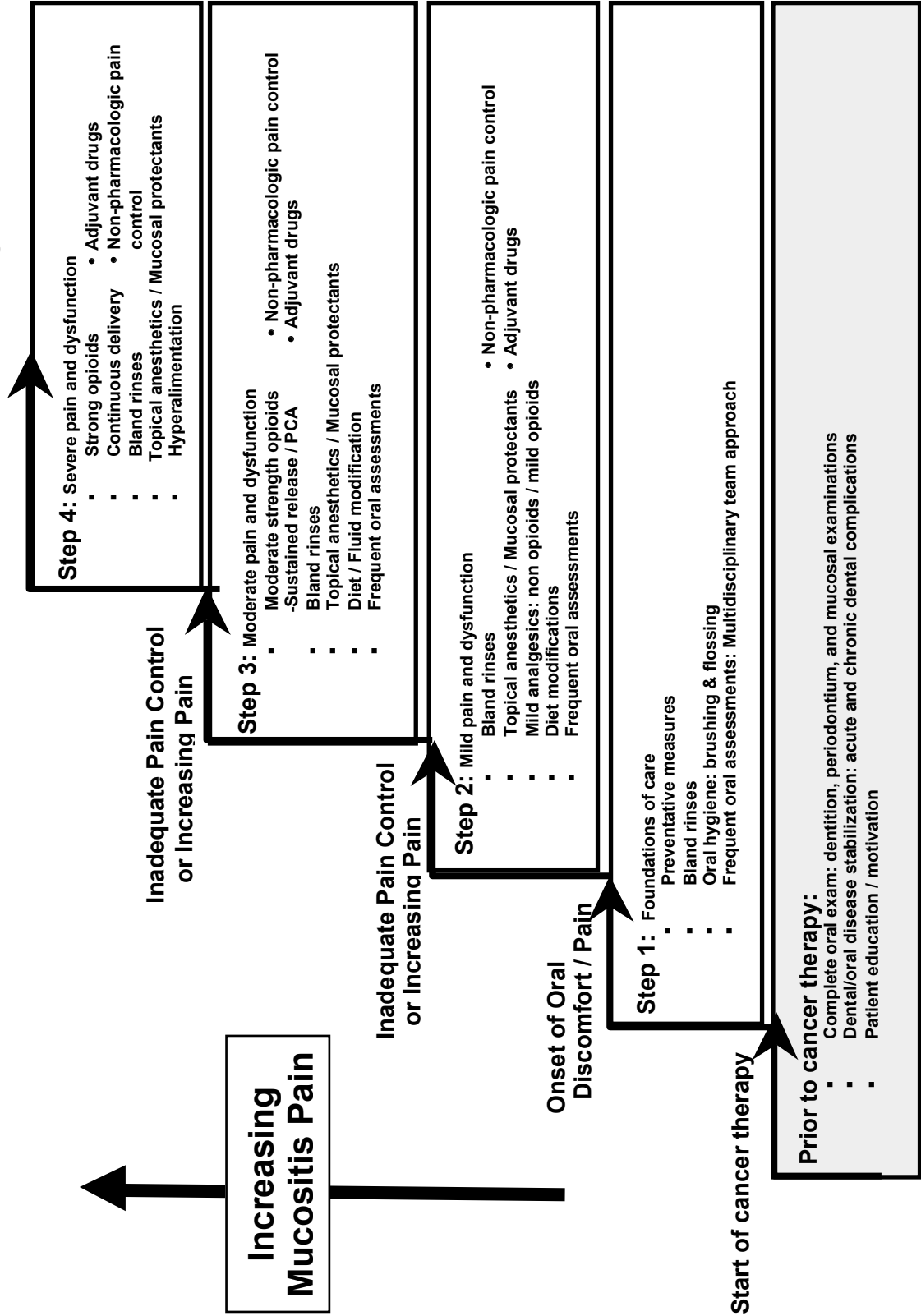
- The basis of acute pain management does not relate to pain intensity, but rather to responses to rising levels of pain and the provision of adequate pain control. The clinician should escalate pain management to the next level when pain control becomes inadequate.
- Start with pain management with strategies that are appropriate for the patient. Start with local topical treatments and escalate as needed.
- The objective of analgesic drug use, especially for opioids, is to achieve the minimum effective analgesic concentration, i.e., the lowest blood level that results in consistent patient report of complete analgesia. Research shows that this level may vary by a factor of 5 across patients. There is no "standard dose" for opioids, as efficacy varies across individuals.
- Once a steady state of adequate pain relief has been achieved, dosing should remain stable until pain assessments show increasing background pain.
- Breakthrough OPM pain should be addressed immediately, usually with aggressive strategies that provide immediate pain relief. This can involve the application of topical anesthetics in combination with a rapid onset short-acting opioids.
- Adjuvant drugs and non-pharmacologic pain management strategies are used at all levels, to enhance pain relief and to treat adverse effects of analgesic medications and to treat concomitant psychological and physiological disturbances such as anxiety, depression and insomnia.
- The drugs recommended for mild-to-moderate pain have dose limits, not because they contain opioids, but primarily because they are combined with acetaminophen or non-steroidal anti-inflammatory drugs that require dose ceilings to avoid toxicity.
- Regular assessment of analgesic adequacy and the adverse effects of analgesic drugs are necessary.

### *Improving Management Success*

There are several common principles that can improve overall management success:

- Anticipate pain problems – be prepared for mucositis pain and commence management at the first recognition of a discomfort.
- Deliver pain medication via the simplest and most convenient manner possible (usually by mouth).
- Dose pain medication on a time-contingent basis, not a pain-contingent basis.
- Utilize a pain management strategy with escalating strength and complexity of pain medications (e.g., the World Health Organization (WHO) "Pain Ladder")
- Customize pain strategies for the individual
- Manage the patient's pain with an attention to detail

# Stepped Approach to Oral Mucositis Pain Management



## MANAGEMENT OF ORAL MUCOSITIS PAIN

Ideally, patients should be assessed prior to therapy as to their level of understanding about mucositis which should be followed up with appropriate education and training. Questions to ask should include the following:

- Do you know what mucositis is?
- Have you had mucositis in the past?
- How was it managed? How successfully was it managed?

If patient has had no experience with mucositis, patient education should include:

- What causes mucositis
- What it feels like
- How long it lasts
- What can be done to prevent it and/or manage it

### STEPPED ORAL MUCOSITIS PAIN MANAGEMENT MODEL

This stepped oral mucositis pain management model is based on principles of ascending aggressiveness of pain management strategies in response to the patient's increasing OPM pain and integrates the basics of oral oncology and dental care with a medical model for managing pain. While based on the principles of the World Health Organization (WHO) analgesic ladder, the integration of a basic oral care foundation step and the consistent use of topical management strategies across steps are unique. This approach initially utilizes a wide variety of oral pain management strategies, including bland rinses and mild analgesic agents (topical anesthetics, non-steroidal anti-inflammatory agents and opioids), but also recommends the use of non analgesic agents (benzodiazepines, antidepressants, etc) and non-pharmacologic pain management strategies (relaxation techniques, TENS, acupuncture and psychological therapy management strategies) when appropriate. An important note to make about this approach to pain management is that when a patient's care is stepped up to the next level, the strategies utilized from the previous step(s) should be continued – for example, bland rinses and topical anesthetics used for mild mucositis pain management should continue to be used after the patient is started on opioids.

*Table 19 Oral Mucositis Pain Control Model*

Elements of Stepped Model for Management of Oral Mucositis Pain	
Pre Cancer Treatment: Oral Health Stabilization	Elimination / Prevention of oral infection and trauma Dental health stabilization: dental decay, periodontal disease, endodontic disease, potential sources of trauma Mucosal health stabilization: elimination of oral infection Patient education and training
Step 1 Foundations of Care	Maintenance of dental and oral health stabilization Routine oral hygiene Bland oral rinses / ice chips Trauma / irritation prevention / Diet modifications Multidisciplinary team: Frequent oral assessments
Step 2	Mild oropharyngeal mucositis pain / oral dysfunction Basic oral hygiene Topical oral pain management Mild analgesics Adjuvant drugs Non-pharmacologic pain control Trauma / irritation prevention Frequent assessments
Step 3	Moderate oral mucositis pain / oral dysfunction Basic oral hygiene (modification as needed) Topical oral pain management Moderate strength opioids Breakthrough pain management Non-pharmacologic pain control Adjuvant drugs Frequent oral assessments of mucositis and oral pain Diet modifications: Nasogastric tube / Hyperalimentation Frequent assessments: oral mucositis and pain
Step 4	Severe oral mucositis pain / oral dysfunction Basic oral hygiene Topical oral pain management Strong opioids: Sustained release / Patient-Controlled Analgesia Breakthrough pain management Non-pharmacologic pain control Adjuvant drugs Frequent oral assessments of mucositis and oral pain Diet modifications: Nasogastric tube / Hyperalimentation Frequent assessments: oral mucositis and pain

**ORAL MUCOSITIS PAIN CONTROL: PRE CANCER THERAPY ORAL AND DENTAL HEALTH STABILIZATION**

The goals for this level are essentially to stabilize oral health, eliminate factors that could complicate the course of cancer therapy and educate and motivate patients relative to oral self-care. It is very important to ensure that patients understand the relationship between oral/dental health and systemic health during cancer treatment. Additionally, strategies to reduce the risk of oral trauma from normal oral function (eating, oral hygiene, etc.) should be reviewed with patients. Basic oral care protocols include plaque control measures (tooth brushing, flossing, etc.), the use of bland oral rinses (normal saline and/or sodium bicarbonate rinses) and the consideration of viral and fungal prophylaxis if patients are at risk for immunosuppression. Potential sources of mucosal irritation from sharp or fractured teeth, broken restorations or poor fitting dentures should also be identified and eliminated.

Finally, patients should be educated as to what oral complications could be associated with the upcoming cancer therapy and how these problems are managed. Patient education should always be instituted prior to initiation of therapy and the onset of symptoms. Information on oral mucositis management should be provided regarding available pain control therapies, including non-pharmacologic options, with the rationale for their use. It is important to discuss the duration and course of symptoms and side-effects. The patient care team should have protocols in place for assessment of mucositis and mucositis management strategies. The patient needs to understand that: 1) it is easier to prevent pain than to reduce it once it has begun, 2) to tell care providers if their pain is not adequately controlled and 3) to factually report pain, while avoiding stoicism or exaggeration.

*Table 20 Foundations of Care*

Oral Hygiene: Bacterial Plaque Control	Tooth Brushing (twice a day) Flossing (once a day) Antibiotic Rinses (when indicated)
Mucosal Moisturizing and Lubrication	Saline rinses Sodium bicarbonate rinses Artificial salivas / Oral moisturizing products
Chapped Lips	Lip balms Lip moisturizing agents Lanolin products
Oral Mucosal and Pain Assessment	Routine mucositis assessment with validated mucosal scoring instrument Oral pain and oral function assessment

**ORAL MUCOSITIS PAIN CONTROL MODEL**

**LEVEL 1: FOUNDATIONS OF CARE**

***Basic Oral Hygiene***

The foundation of oral care for cancer patients centers on maintaining basic dental and gingival health and mucosal integrity throughout cancer treatment periods. Patients should continue oral hygiene protocols to remove bacterial dental plaque with tooth brushing and flossing regimens. Oral bacteria can negatively influence ulcerative mucositis and periodontal infections (gingivitis, periodontitis, etc) and can lead to both local and systemic infection problems for patients, especially if they become immunosuppressed. Antibiotic oral rinses (e.g., chlorhexidine oral rinses) can be used to control bacterial plaque when brushing or flossing is compromised. As mouth pain increases, oral hygiene protocols may need to be modified, e.g., having patients discontinue the use of toothpaste if it causes stinging, encouraging the use of floss holders for patients with mucositis or if flossing with hands is associated with nausea and vomiting.

***Bland Oral Rinses***

Bland rinses are useful for moisturizing the mouth, reducing mucosal irritation and reducing discomfort. Numerous rinses containing various combinations of ingredients have been recommended. Recent evidence indicates, however, that perhaps normal saline solution (0.9%) is the best. Dodd, et al (2001), found that normal saline solution was as effective as “magic mouthwash” (lidocaine, diphenhydramine, antacid solutions and nystatin) in reducing mucositis pain and was also better than chlorhexidine. The conclusion was that the least expensive, safest and easiest to use compound – normal saline solution – was the treatment of choice.

## MANAGEMENT OF ORAL MUCOSITIS PAIN

Examples of bland oral rinses include:

- 0.9% saline solution (0.9 gm NaCl in 100 ml water – approximately ¼ tsp in 8 oz. water). In most instances, sterile saline is not necessary unless there is concern for the safety of water supply. Rinse containers should be changed daily or thoroughly cleaned. Ice can be added to the saline solution immediately before rinsing if the coolness is more comfortable for the patient. Sucking on ice chips can also be of benefit for many patients due to their “counter stimulation” effect.
- Sodium bicarbonate rinses (1-2 Tbls in 32 oz. water) – especially recommended after emesis, to neutralize gastric acid and buffer oral pH
- 0.9% Saline + sodium bicarbonate rinses – (0.9% saline has a pH of 5.2, adding sodium bicarbonate will increase the pH to a more neutral to slightly basic pH)

### **Oral Rinsing Instructions:**

- Swish and gargle solution for 12-30 seconds per mouthful
- Use a total of 12-16 oz., every 6 hours or as often as every 15-30 minutes as necessary to provide for patient comfort
- Use rinses prior to application of medicated rinses or topical medications, to remove mucus saliva and debris

### **Oral Moisturizing and Lubrication**

Since salivary gland dysfunction is frequently noted with cancer chemotherapy and head and neck radiation, bland rinses can be instituted when this occurs to help moisturizing mucosal surfaces, keeping the mouth clear of debris and stimulating salivary function to maintain oral comfort. Artificial salivas and oral moisturizing products can help patients remain more comfortable. The swishing and expectorating of antacid solutions (e.g., Amphojel<sup>®</sup>) to coat oral tissues have not been adequately studied to determine efficacy, but could be hypothetically of benefit, especially in instances of emesis.

### **Chapped Lip Management**

Chapped lips are also a common complication of intensive cancer chemotherapy protocols. The use of lip balms and moisturizing agents should be encouraged early on to prevent potential cracking and splitting of the patient's lips. Lanolin cream or ointment can often provide for better lip protection than petroleum-based products.

### **Oral Mucositis and Mucositis Pain Assessment**

Oral assessments for mucositis should begin early after the start of cancer treatment protocols and be repeated on a regular basis. A multidisciplinary team approach to assessing and managing oral care is strongly recommended to assure continuity and completeness of care.

A number of instruments have been developed to assess clinical oral status and range from simple scales such as the WHO Mucositis Scale, to more complicated research orientated instruments such as the Oral Mucositis Index; the choice of which instrument to use is primarily based on the intended use of gathered scores and the practicality of who will be assessing the patient where training and issues of inter-rater reliability are the primary issues.

### **Oral Infection Prophylaxis**

Though technically not part of a mucositis prevention or management protocol, patients at risk for significant myelosuppression from cancer therapies and thus oral viral and fungal infections, will often be placed on infection prevention protocols that include antiviral, antifungal and antibacterial agents. Oral infections, especially herpes simplex infections in this setting, can significantly amplify mucosal breakdown and oral pain. If patients are not treated with infection prophylaxis protocols they should be carefully monitored for the possible occurrence of infection, the presence of which can be masked by the “expected” mucositis.

## **ORAL MUCOSITIS PAIN CONTROL MODEL**

### **LEVELS 2-4: MILD TO SEVERE ORAL MUCOSITIS PAIN AND ORAL DYSFUNCTION**

Oral mucositis related discomfort and pain often is first noted as pharyngeal discomfort (“sore throat”) and then progresses to oral symptoms. Patients should increase their frequency of rinsing with bland rinses and be started on topical anesthetics and, when medically possible, mild non-opioid analgesics. The use of the NSAIDs is contraindicated where concerns for bleeding due to anticoagulation or low platelet counts are present. The addition of mucosal protectants, adjuvant drugs and non-pharmacologic pain control measures should also be considered. Additionally, modifications to the patient's diet should be encouraged that include softer and moister foods. Oral examinations and subjective assessments should document the extent of mucosal damage, level

and direction of pain, and overall patient comfort and satisfaction with current management strategies.

With increasing pain, oral mucositis pain management efforts should become more focused on the use of opioids. Initially mild opioids are used, but should be quickly escalated to the use of stronger opioids, often with continuous dosing with time-release formulations, patches, intravenous, intramuscular or subcutaneous parenteral dosing. The use of patient-controlled analgesia (PCA) requires a specific computerized infusion pump apparatus, and though technically more complicated to set up, provides an excellent strategy for pain medication delivery; studies have shown patients to use a lower total opioid dose with better pain control and fewer opioid side-effects.

Basic oral hygiene should be continued. If toothpaste becomes irritating, patients should be switched to non-mint flavored toothpastes or instructed to brush with saline or water only.

**Topical Management of Mucositis Pain**

Topical management of oral mucositis pain utilizes bland oral rinses, mucosal protectants and bland coating and moisturizing agents.

**Bland Rinses**

The frequency of bland rinses should be increased as oral discomfort increases. Rinses should be made available bedside so that they can be used ad lib. A cup of saline should be easily available at bedside to be swished and spit should the patient wake with mouth discomfort. The soothing effect can help the patient go back to sleep more readily.

**Topical Anesthetics**

The use of topical anesthetics is recommended early in the evolution of mucositis, to manage mild to moderate mucositis pain. The anesthetic should be applied directly to painful tissues in sufficient concentrations, and held in the mouth for a long enough time, to allow penetration to reach nerve endings and provide for significant anesthesia. Frequency of subsequent applications depends on which anesthetic is being used, how it is applied, and the severity of mucositis. As mucositis worsens, the effective duration of anesthesia will become shorter. However, use should continue as the patient moves up the pain control ladder. As there are relatively few comparative trials of topical efficacy, the clinician will have to rely on clinical experience and patient acceptance when choosing which drug to use and how to apply it.

*Table 21 Topical Anesthetics for Management of Mucositis Pain*

Agent	Formulations
<b>True Topical Anesthetics</b>	
Lidocaine	Viscous gel, Jelly, Ointment, Solution, Patches
Benzocaine	Gel, Ointment, Spray
Tetracaine/Chirocaine	Anesthetic tabs
EMLA	Cream
“Magic Mouth Rinses”	Compounded rinse (lidocaine, diphenhydramine, Amphojel, +/- nystatin)
<b>Antihistamines</b>	
Diphenhydramine	Elixir, IV solution
<b>Other Agents</b>	
Doxepin	Elixir
Benzylamine	Rinse (not available in US)
Benzonatate	Gel caps (open and coat mouth)
Cocaine	Compounded 10% solution

Probably one of the most frequently prescribed treatments for oral mucositis are the so-called “Magic Mouth Washes.” These rinses represent an empiric combination of a number of agents including anesthetics (lidocaine and diphenhydramine) together with an antacid “coating” agent (e.g., Amphojel®), an antifungal (e.g., Nystatin) and occasionally a steroid. While these compounded rinses can clearly provide for palliative pain control due to the topical anesthetics, their efficacy remains equivocal and there is insufficient evidence to suggest that they are any more effective than topical anesthetic agents used signally. Additionally, the efficacy of antacid coating agents, nystatin and steroids in this setting has never been proven, especially in the more common concentrations. It is worth noting that topical nystatin rinses have been definitively shown to be ineffective in preventing oral Candida infection in oncology settings, so there is even less reason to believe nystatin provides any benefit in the setting of this mucositis treatment.

## MANAGEMENT OF ORAL MUCOSITIS PAIN

When considering the use of such compounds, the following questions should be asked:

- Are all the agents in the rinse indicated for the situation and are they efficacious?
- Does the combination provide any more benefit than a single agent?
- Are all the agents in the compound accepted by the patient? Many patients find the taste and/or consistency of these combination rinses unacceptable.
- Is the best formulation of the drug being used?
- What is the cost/benefit ratio for these rinses, given that compounding is more expensive?

When doxepin, an antidepressant, is applied topically in liquid form it initially causes anesthesia, but as the anesthesia wears off there can be a persistent analgesic effect. This is a phenomenon that is similarly noted for benzydamine rinses (benzydamine is not available in the US, but is marketed in Canada, Europe and South America). Both diphenhydramine solutions and doxepin elixir can produce some degree of sedation and oral dryness if swallowed. Cocaine is a powerful topical anesthetic, which has not been prescribed very much in recent years due to its reputation as a drug of abuse, but which nonetheless is potentially useful in this setting. In addition to producing rapid anesthesia, it is also a strong vasoconstrictor, which makes it useful for mucositis patients with mucosal bleeding problems. There can be some central effects from topical oral mucosal application, although the mild euphoria experienced can be beneficial for patient mood and the potential for abuse in mucositis patients is generally not an issue.

Warning: Mucositis patients being treated with topical anesthetics should be cautioned to:

- Avoid accidental mucosal trauma when tissues are numb
- Not to eat or perform oral hygiene while oral tissues are anesthetized
- Not to wear removable oral appliances
- Be especially careful not to gargle or swallow anesthetics – anesthesia of the soft palate/ oropharynx can diminish the patient's gag reflex and increase the risk of aspiration
- Do not swallow topical anesthetics unless they are safe relative to potential systemic effects and they are deemed acceptable.

### **Mucosal Surface Protectants**

A number of proprietary agents with mucosal covering or mucoadherent effects are marketed to help with the management of oral mucositis, some with "prophylactic use" protocols. While these products have been approved as "devices" by the FDA (e.g., Gel Clair<sup>®</sup>, Mucotrol<sup>™</sup>, MuGard<sup>™</sup>, CAPHOSOL<sup>®</sup>); unfortunately there is minimal or no scientific evidence to demonstrate clinical efficacy for these products, and until there is adequate supportive research, they cannot be recommended. Film-forming agents (e.g., hydroxypropylcellulose gels and 2-octyl cyanoacrylate products) provide a thin adherent barrier over ulcerated tissue, thereby reducing some of the stimulation and reducing pain.

## PHARMACOLOGIC PAIN CONTROL

Systemic pharmacotherapy currently provides the foundation for treating moderate or severe oral mucositis, as it is low risk, cost effective, dependable and easily administered. The value in starting with and maintaining topical and non-pharmacological therapies along with cognitive and behavior interventions lies in the ability to provide the dual benefits of pain control and coping strategies. A multimodal approach maximizes the effectiveness of pain control and reduces the need for otherwise more aggressive single modality pain therapies. Treatment must be individualized, as patients vary in acceptance of, and responses to, specific analgesics and adjuvants as well as different behavioral strategies.

### **Systemic Analgesics**

The major classes of analgesic drugs used in treatment of cancer-related pain include the non-steroidal anti-inflammatory drugs (NSAIDs), opioids and adjuvant analgesics. The various routes of drug delivery used include both enteral (oral, transmucosal) and parenteral (intramuscular, subcutaneous and intravenous) routes.

### **Non-opioid Analgesia: NSAIDS**

The major class of analgesics recommended for mild oral mucositis pain are the non-steroidal anti-inflammatory drugs. They are effective when used alone or when combined with opioids. These drugs bind to different receptors than do the opioids and affect the tissue damage and pain caused by inflammation. They provide enhanced analgesia when used with opioids, as the resultant effect is more than simply an additive effect. The advantages of the NSAIDs include the fact that many are available OTC, making them relatively inexpensive, and that they do not produce tolerance or dependence. There is, however, a ceiling effect on both analgesic

potential and toxicity and thus maximum safe dose limits must be adhered to – a factor that is critical to consider when they are combined with opioids. The safe maximum dose for the NSAID component of the combination agents can often be reached well before reaching the maximum dose of the opioid agent. While technically not an NSAID, acetaminophen is included in this group due to its analgesic action and general safety level.

**Table 22 Non-Steroidal Anti-Inflammatory Drugs**

Paracetaol	Acetaminophen
Propionic acids	Ibuprofen, Naproxen, Naproxen sodium, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin
Meclofenamic acid	Meclomen
Acetic Acids	Diclofenac potassium, Sulindac, Ketoralac, Etodolac
Nonselective COX-1 and COX-2 Inhibitors	Aspirin, Diflunisal, Choline magnesium trisalicylate
Selective COX-2 Inhibitors	Celecoxib (see FDA alert)
Cox / Lox Inhibitor	Llicofelone (under development)
Oxicams	Piroxicam, Tenoxicam, Droxicam, Lomoxicam, Meloxicam

**Spectrum of NSAID Toxicity**

Platelet dysfunction is the most problematic side effect of NSAIDS, and they should not be given to patients at risk for bleeding problems, e.g., thrombocytopenic patients or patients with a history of bleeding gastric or duodenal ulcers, etc. The side-effect of greatest concern however, is renal and hepatic toxicity, especially with extended use. NSAIDS bind to plasma proteins and may displace other protein-bound drugs, thus altering the availability and effectiveness of drugs such as warfarin, methotrexate, digoxin, cyclosporin, oral anti-diabetic agents and sulfa drugs. NSAIDS are typically available in a variety of dosing forms, including tablets, caplets, capsules, oral liquids and rectal suppositories. Choice of drug and dosage may be based on patient response and titrated to effect.

**Opioids**

The opioids are the cornerstone for moderate to severe mucositis pain management. These drugs are effective, easy to titrate and have a favorable risk/benefit ratio. There is no ceiling to their analgesic efficacy. There are two major categories of opioid drugs: those used for control of mild to moderate pain and those used for control of moderate to severe pain. The efficacy and potency of these drugs is dependent upon the delivery system, and when they are formulated with NSAIDs, the latter agent can limit their dosage.

**Opioids: Formulations**

The oral dose of these drugs can provide for immediate, intermediate and extended release. The latter are often the most popular formulations, as they can provide longer periods of sustained pain relief, and can also result in better compliance with “by the clock” dosing. While oral is generally the preferred route of analgesia administration, other routes (transdermal, transmucosal or parenteral) may be considered. By utilizing different routes and formulations of agents throughout the day, an effective pain relief protocol can often be developed to keep a patient comfortable while both awake and during sleep. Recent studies have established the benefit of transdermal Fentanyl in managing severe oral mucositis. Additionally, the rapid uptake of oral transmucosal fentanyl makes it a reasonable consideration for use for breakthrough oral mucositis pain; combination with other opioids requires careful adjustment of doses and monitoring for side-effects.

**Dosage of Opioid Analgesics**

Patients vary greatly in analgesic dose requirements and responses to opioids, thus the recommended protocol specifies standard starting doses, followed by titration of subsequent doses, as the analgesic and side effects are monitored.

For many opioids, it is may be possible to reduce the amount of opioid needed to control oral mucositis pain by combining the opioid with a medication with analgesic-sparing properties, also referred to as a potentiator. Hydroxyzine is probably the most effective and safest opioid potentiator. Orphenadrine and other antihistamines, nefopam (a non-opioid analgesic available in Europe), and the muscle relaxant carisoprodol, and antihistamines can also be used to potentiate most opioids. It is extremely important that the titration of opioids and addition of the potentiator be very carefully supervised, especially in the case of carisoprodol.

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Table 23 Oral Mucositis Pain Control: Level III and IV

Opioid Medications for Oral Mucositis: Steps 2 - 4	
Mucositis Management Step	Standard Starting Dose / Route <sup>1</sup>
Steps 2 and 3: Opioids for Mild to Moderate Mucositis Pain	
Codeine phosphate <sup>2</sup> Codeine sulfate <sup>2</sup> Oxycodone <sup>2</sup> Oxycodone extended release tabs <sup>2</sup> Hydrocodone <sup>2</sup>	15 – 60 mg PO/SC/IM q4-6 hr 15 – 60 mg PO q4-6hr 15 – 30 mg PO q4hr 10 – 160 mg PO q12hr 5 – 10 mg PO q4-6 hr
Steps 3 and 4: Opioids for Moderate to Severe Mucositis Pain	
Morphine oral Morphine extended release Morphine IV, IM	10-60 mg PO 15-30 mg PO q8-12 hr Intravenous doses can vary from 1-7 mg/hour (IV direct: 1-5 mg given over at least 1 minute, titrated every 6-10 minutes until analgesia is achieved (usual maximum 12 mg per hour), then give IM, SC, IV intermittent or IV/SC infusion: IM, SC: 5-10 mg q3-4h IV intermittent: 5-10mg given over 15-30 minutes q3-4h IV, SC infusion: 0.5-4 mg/hr titrated to effect; there is no maximum dose
Hydromorphone	2-8 mg PO q3-4 hr; 1-4 mg SC / IM / IV
Oxycodone <sup>2</sup> Oxycodone extended release <sup>2</sup>	15-30 mg PO q4 hr 10-160 mg PO q12 hr
Oxymorphone <sup>2</sup> Oxymorphone extended release <sup>2</sup> Oxymorphone <sup>2</sup>	10-20 mg PO q4-6 h 5 – 40 mg PO q12hr 1 – 1.5 mg SC / 2.5-5 mg SC/ IM /IV q8-12 hr
Methadone	2.5-10 mg PO bid or t.i.d. / 10 mg IM 2 mg PO / 2 mg IM
Levorphanol	2 mg PO q6-8hr
Fentanyl transdermal patch Fentanyl Intravenous Fentanyl transmucosal <sup>3</sup> Fentanyl buccal tablet <sup>3</sup>	12-1000 mcg/h patch q72hr 100 µg 50-100 mcg/kg IV q1-2hr or 0.5-1.5 mcg/kg/IV 100 - 200 mcg per dose (titrate q15 minutes p.r.n.) 100 – 800 mcg applied to buccal gingiva
<b>Not recommended: These drugs are either antagonists or agonist drugs with poor profiles for extended use</b>	<b>Not recommended</b>
Meperidine Propoxyphene Tramadol Talwin Pentazocine	Buprenorphine Pentazocine Butorphanol Dezocine Mereridine Nalbuphine

1 Adult dosing schedules. Doses need to be adjusted depending on renal and/or hepatic status

2 Are combined with acetaminophen, aspirin, or ibuprofen which can be dose-limiting

3 Transmucosal and buccal fentanyl are used for breakthrough pain, doses can vary and are customized by prescribing clinician

### Side-Effects of Opioids

One of the major drawbacks to the use of opioid drugs for pain control is the potential development of tolerance, which is a physiologic state in which the patient requires increased doses of the drug to achieve the same analgesic effect. Fortunately, tolerance is more of a consideration for long-term use of these drugs and not usually a problem for opioid-naïve mucositis patients.

Physical dependence is an expected state of adaptation, not an adverse side-effect to opioid analgesics that can develop and is due to the pharmacologic properties of opioids, producing an “abstinence syndrome”. It occurs when a patient becomes adapted to an agent that when withdrawn can cause distinct side effects. Physical dependence is often confused with addiction.

The signs and symptoms of physical dependence include:

- Anxiety
- Lacrimation
- Abdominal cramps
- Irritability
- Rhinorrhea
- Vomiting
- Chills and hot flashes
- Diaphoresis
- Diarrhea
- Joint pain
- Nausea

Dependence tends to occur after 2 weeks of opioid therapy, and withdrawal symptoms may be avoided by gradually decreasing the scheduled frequency of the opioid.

Addiction is a term that is often mistakenly applied to physical dependence side-effects associated with opioid use for pain control. Addiction involves a psychological dependence, characterized by overwhelming involvement with drug use, compulsive use and behavior directed toward securing a supply of drug. In addicted individuals, there is a high tendency to relapse into drug abuse, despite the obvious harm and social consequences that result. In contrast to true addiction, what is more commonly encountered in patients using opioids for pain control is pseudo-addiction, which is the result of inadequate opioid dosage, leading to increased sympathetic nervous system activity and a need for increased medication.

### ***Management of Side Effects of Opioid Therapy***

When prescribing opioids, side-effects should be anticipated. The most common side-effects that interfere with opioid dosing are constipation, nausea, pruritus, and sedation. Other side effects that are encountered include fatigue, vomiting, confusion, urinary retention, myoclonus, dysphoria, euphoria, sleep disturbance, sexual dysfunction, respiratory depression, and endocrine abnormalities. Persistent respiratory depression is rare in opioid-tolerant individuals. Generally, most side-effects will occur in the first few hours of treatment and then will gradually disappear. If side-effects persist, the clinician may choose to switch a patient's pain medication to make sure the patient gets maximum pain control with a minimum of side-effects. Dehydration can accentuate the side-effects of opioids, so patients should be encouraged to drink adequate fluid volumes or these should be provided intravenously when necessary.

Strategies to manage side effects of opioid therapy can include:

- Change the dosing regimen or route of the same drug – aim for constant blood levels and avoiding high serum peak levels.
- Try another opioid that may have a different propensity for producing a specific side-effect.
- Add drugs to regimen to counteract specific adverse effects.
- Constipation: Anticipate this very common problem caused by opioids. Prevention revolves around the following:
  - Encouraging patients to drink plenty of fluids
  - Use of high fiber diets
  - Administering bowel stimulants and stool softeners on a regular basis.

If constipation develops, treatment usually requires the use of enemas and/or suppositories. Magnesium citrate is used for impaction in the proximal colon. Opioid-induced ileus is managed with continuous infusion of metoclopramide.

**Nausea and vomiting:** Normally, these side effects occur a day or two after first taking a particular medicine and correlate to high serum peak levels. Consequently, aiming for relatively constant blood levels can help reduce nausea. Different opioids in different patients can cause variable degrees of nausea – therefore consider an alternative opioid. The prophylactic use of antiemetics can reduce or prevent this side-effect. Transdermal scopolamine, hydroxyzine or phenothiazine can be used until tolerance to nausea develops.

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**Sedation:** When first taking opioids, some patients may feel drowsy or sleepy, however, it is usually only transient and for most patients will disappear in a day or two. If this is a serious problem, several strategies can be employed:

- Decreasing the dose and increasing the frequency of administration
- Switching to an opioid with a shorter half-life
- Opioid rotation, or
- Administration of centrally acting stimulants such as caffeine, methylphenidate, or amphetamines.

**Pruritus (itching):** Changing opioids can usually help eliminate this problem. Oxycodone and fentanyl have little propensity to release histamine, which often causes itching or urticaria. Additionally, antihistamines can be used to manage this side effect of opioid administration. Antihistamines can also augment analgesia and help reduce anxiety.

**Respiratory depression:** Respiratory depression is probably the best example of a serious adverse pharmacological effect that is only rarely encountered clinically, but which generates concern sufficient to cause under-treatment. The occurrence of respiratory depression is extremely uncommon in patients who undergo gradually escalating doses. It can however, occur in opioid-naïve patients who receive high doses of opioid analgesics. Opioid-induced respiratory depression, if not caused by a massive overdose, is always heralded by the gradual onset of obtunded and/or slowed respiratory rate, signs that signal an impending problem that needs to be managed appropriately. Monitoring drug effects by assessing the level of consciousness and respiratory rate can greatly diminish the risk of serious respiratory depression.

### **Adjuvant Drugs**

Adjuvant pharmacotherapy is used to augment analgesia, to treat psychological disturbances and distress and to treat the adverse effects of primary analgesic drugs. This is a diverse group of drugs and often utilizes antidepressants and anti-anxiety agents, and can be more difficult to use without some level of experience.

Adjuvant analgesia frequently utilizes low-dose tricyclic antidepressants (TCAs). While the most recognized pain management arena for these agents is for chronic pain, they can also be used advantageously for short-term pain situations, too, especially where mucositis is a recurrent problem with successive rounds of cancer treatment. The value of these drugs for patients with mucositis is clearly not in providing an antidepressant effect but rather to aid with sleep dysfunction and relaxation. These drugs bind centrally to non-opioid receptors and in this situation it is accepted that they have no antidepressive effect per se. Due to their “anticholinergic-like” effect, TCAs may produce adverse side effects such as xerostomia, sedation and occasionally constipation. Although rare, there also is a risk for marrow suppression.

The other major group of drugs in this category are anti-anxiety agents with such agents as lorazepam, diazepam and alprazolam. Standard precautions relative to the use of these agents definitely need to be followed in this setting.

*Table 24 Adjuvant Drugs*

Tricyclic antidepressants	Favored because of weaker anticholinergic effect
Selective serotonin re-uptake inhibitors	Can be used, but have not been adequately researched, and generally do not help with sleep
Antihistamines	Enhance opioid analgesia Help manage anxiety Provide sedation Reduce opioid-related itching
Benodiazepines	Useful to relax patients when anxiety contributes to mucositis pain experience

**Non-pharmacologic Management of Pain**

Non-pharmacologic techniques for pain management represent a wide range in supportive care pain management strategies. Several of these techniques require specific training prior to the onset of pain and ongoing supervision and support can increase their effectiveness. Strategies include:

- Exercise
- Counter-stimulation – ice packs, massage, and heat applied to perioral/head and neck areas
- Pediatric patients – holding, stroking and rubbing
- Transcutaneous electrical nerve stimulation (TENS)
- Acupuncture
- Cognitive-behavioral strategies
- Distraction and reframing
- Relaxation and guided imagery
- Hypnosis
- Psychosocial Interventions
- Peer support groups – particularly if pain is of longer duration
- Pastoral counseling – spiritual care and support system for patients and family
- Pediatric patients need more help – the parents must also be educated and involved.

**SPECIAL CONSIDERATIONS: ELDERLY PATIENTS**

The clinician must be cognizant of the fact that the elderly often have many chronic problems, and be aware of patient confusion and/or difficulty with comprehension. While there are misconceptions about aging and pain, the clinician must learn to recognize symptoms of hearing or vision changes, as well as cognitive impairment, delirium or dementia that may be present in older patients. By recognizing these problems and making appropriate modifications to analgesic regimens, both NSAIDs and opioids can be used safely in a geriatric population.

**SPECIAL CONSIDERATIONS: PEDIATRIC PATIENTS**

There are a number of important misconceptions about pain and pain management in children:

- Children of all ages experience pain just as adults do, and they do remember the pain.
- Children can communicate and describe their pain.
- Pain in children is multidimensional, just as it is in adults – emotion, cultural and spiritual beliefs, environmental factors, behaviors, cognition and development can all influence the pain experience for the child.
- Behavioral and expressive aspects of pain may not be as evident in children, especially when the pain is chronic – you need to ask the child how and what they are feeling.
- It is no surprise to dentists: pain can affect a child's future development.

Pediatric pain management principles are very similar to those used for adults. Pain management protocols should look to treat with the least invasive route possible and utilize appropriate combinations of opioids plus non-opioids and adjunctive therapy. When pain is anticipated and/or ongoing, medication should be given around the clock to provide steady-state analgesia. Appropriate analgesic therapy should be available for any breakthrough pain. When determining dosage levels of analgesics, titrate pain medications to effect – use as much as needed, not as little as possible.

Children can suffer from the side effects of pain management protocols and these should be anticipated and managed quickly – constipation, nausea, vomiting, itching, and sedation. Non-pharmacologic management strategies can help relieve pain – relaxation (including a soothing environment with less noise and light), imagery, distraction, massage, etc. all help. Involve child-life specialists in customizing the care approach for the child. Educate the patient and family to know that pain is to be treated, not tolerated. Both patient and family are essential for pain assessment and determining the success of pain management strategies.

**SUMMARY**

Effective pain control for mucositis requires constant attention and willingness on the part of managing clinicians to evaluate and adapt pain-relieving strategies throughout the period of risk for oral mucositis. By utilizing the principles of an individualized, tiered approach to pain management, that addresses the multidimensional components of a patient's pain, maximum comfort can be consistently provided while reducing the risk for side effects.

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**PEDIATRIC MANAGEMENT**

**AMERICAN ACADEMY OF PEDIATRIC DENTISTRY GUIDELINE ON  
DENTAL MANAGEMENT OF PEDIATRIC PATIENTS RECEIVING  
CHEMOTHERAPY, BONE MARROW TRANSPLANTATION AND/OR RADIATION**

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**PURPOSE**

The American Academy of Pediatric Dentistry recognizes that the pediatric dental professional plays an important role in the diagnosis, prevention, stabilization, and treatment of oral and dental problems that can compromise the child's quality of life before, during, and after cancer treatment. Dental intervention with certain modifications must be done promptly and efficiently, with attention to the patient's medical history, treatment protocol, and health status.

Chemotherapy and/or radiotherapy for the treatment of cancer or in preparation for hematopoietic cell transplantation (HCT) may cause many acute and long-term side effects in the oral cavity. Furthermore, because of the immunosuppression the patients experience, any existing or potential sources of oral/ dental infections and or soft tissue trauma can compromise the medical treatment, leading to morbidity, mortality, and higher hospitalization costs. It is imperative that the pediatric dentist be familiar with the oral manifestations of the patient's underlying condition and the treatment differences for patients undergoing chemotherapy only and those who will receive an HCT.

**METHODS**

This guideline is based on a review of the current dental and medical literature related to dental management of pediatric patients receiving chemotherapy, hematopoietic cell transplantation, and/or radiation. A MEDLINE search was conducted using the terms "pediatric cancer", "pediatric oncology", "hematopoietic cell transplantation", "bone marrow transplantation", "mucositis", "stomatitis", "chemotherapy", "radiation therapy", "acute effects", "long-term effects", "dental care", "pediatric dentistry", and "clinical practice guidelines". Expert opinions and best current practices were relied upon when sufficient scientific data were not available.

**BACKGROUND**

The most frequently documented source of sepsis in the immunosuppressed cancer patient is the mouth; therefore, early and definitive dental intervention, including comprehensive oral hygiene measures, reduces the risk for oral and associated systemic complications.<sup>1-13</sup> All patients with cancer should have an oral examination before initiation of the oncology therapy, and treatment of preexisting or concomitant oral disease is essential to minimize complications in this population.<sup>6</sup> The key to success in maintaining a healthy oral cavity during cancer therapy is patient compliance. The child and the parents should be educated regarding the possible acute side effects and the long-term sequelae of cancer therapies in the oral cavity.<sup>1-6,8,14-16</sup> Younger patients present more oral problems than adults.<sup>2</sup> Because there are many oncology and HCT protocols, every patient should be managed on an individual basis and appropriate consultations with physicians and other dental specialists should be sought before dental care is instituted.<sup>5</sup>

## RECOMMENDATIONS

### *Dental and oral care before the initiation of cancer therapy*

#### **Objectives**

The objectives of a dental/oral examination before cancer therapy starts are two-fold<sup>16</sup>:

1. to identify and stabilize or eliminate existing and potential sources of infection and local irritants in the oral cavity—without needlessly delaying the cancer treatment or inducing complications; and
2. to educate the patient and parents about the importance of optimal oral care in order to minimize oral problems/discomfort before, during, and after treatment and about the possible acute and long-term effects of the therapy in the oral cavity and the craniofacial complex.

#### **Initial Evaluation**

Medical history review: should include, but not be limited to, type of disease/condition, treatment protocol, medications (including bisphosphonates), allergies, surgeries, secondary medical diagnoses, and immunosuppression status. For HCT patients, include type of transplant, matching status, donor, conditioning protocol, and graft versus host disease (GVHD) prophylaxis. The American Heart Association (AHA) recommends that antibiotic prophylaxis for non-valvular devices, including indwelling vascular catheters (i.e., central lines) is indicated only at the time of placement of these devices in order to prevent surgical site infections.<sup>17</sup> The AHA found no convincing evidence that microorganisms associated with dental procedures cause infection of non valvular devices at any time after implantation.<sup>17</sup> The infections occurring after device implantation most often are caused by staphylococcal Gram-negative bacteria or other microorganisms associated with surgical implantation or other active infections. The AHA further states that immunosuppression is not an independent risk factor for non-valvular device infections; immunocompromised hosts who have those devices should receive antibiotic prophylaxis as advocated for immunocompetent hosts.<sup>17</sup> Consultation with the child's physician is recommended for management of patients with non-valvular devices.

**Dental history review:** includes information such as habits, trauma, symptomatic teeth, previous care, preventive practices, etc.

**Oral/dental assessment:** should include thorough head, neck, and intraoral examinations, oral hygiene assessment and training, and radiographic evaluation based on history and clinical findings.

#### **Preventive Strategies**

**Oral hygiene:** Oral hygiene includes brushing of the teeth and tongue 2 to 3 times daily with regular soft nylon brush or electric toothbrush, regardless of the hematological status.<sup>4,5,8,9,13,18</sup> Ultrasonic brushes and dental floss should be allowed only if the patient is properly trained.<sup>1,8</sup> Patients with poor oral hygiene and/or periodontal disease may use chlorhexidine rinses daily until the tissue health improves or mucositis develops. The high alcohol content of commercially-available chlorhexidine mouthwash may cause discomfort and dehydrate the tissues in patients with mucositis; thus, an alcohol-free solution is indicated in this situation.

**Diet:** Dental practitioners should encourage a non-cariogenic diet and advise patients/parents about the high cariogenic potential of dietary supplements rich in carbohydrate and oral pediatric medications rich in sucrose.

**Fluoride:** Preventive measures include the use of fluoridated toothpaste, fluoride supplements if indicated, neutral fluoride gels/rinses, or applications of fluoride varnish for patients at risk for caries and/or xerostomia. A brush-on technique is convenient and may increase the likelihood of patient compliance with topical fluoride therapy.<sup>8</sup>

**Trismus prevention/treatment:** Patients who receive radiation therapy to the masticatory muscles may develop trismus. Thus, daily oral stretching exercises/physical therapy should start before radiation is initiated and continue throughout treatment. Therapy for trismus may include prosthetic aids to reduce the severity of fibrosis, trigger-point injections, analgesics, muscle relaxants, and other pain management strategies.<sup>3,5,10</sup>

**Reduction of radiation to healthy oral tissues:** In cases of radiation to the head and neck, the use of lead-lined stents, prostheses, and shields, as well as salivary gland sparing techniques (e.g., 3-dimensional conformal or intensity modulated radiotherapy, concomitant cytoprotectants, surgical transfer of salivary glands), should be discussed with the radiation oncologist.

**Education:** Patient/parent education includes the importance of optimal oral care in order to minimize oral problems/discomfort before, during, and after treatment and the possible acute and long-term effects of the therapy in the craniofacial complex.

### **Dental care**

#### **Hematological Considerations:**

1. Absolute neutrophil count (ANC)
  - $>1,000/\text{mm}^3$ : no need for antibiotic prophylaxis.<sup>10</sup> However, some authors<sup>5</sup> suggest that antibiotic coverage (dosed per AHA recommendations<sup>19</sup>) may be prescribed when the ANC is between 1,000 and  $2,000/\text{mm}^3$ . If infection is present or unclear, more aggressive antibiotic therapy may be indicated and should be discussed with the medical team
  - $<1,000/\text{mm}^3$ : defer elective dental care until the ANC rises. In dental emergency cases, discuss antibiotic coverage beyond endocarditis prophylaxis with medical team before proceeding with treatment. The patient may need hospitalization for dental management.<sup>12</sup>
2. Platelet count<sup>5,10</sup>
  - $>75,000/\text{mm}^3$ : no additional support needed but the dentist should be prepared to treat prolonged bleeding by using sutures, hemostatic agents, pressure packs, gelatin foams, etc.
  - 40,000 to  $75,000/\text{mm}^3$ : platelet transfusions may be considered pre- and 24 hours post-operatively. Localized procedures to manage prolonged bleeding may include sutures, hemostatic agents, pressure packs, and/or gelatin foams.
  - $<40,000/\text{mm}^3$ : defer care. In dental emergency cases, contact the patient's physician to discuss supportive measures (e.g., platelet transfusions, bleeding control, hospital admission) before proceeding.
3. Other coagulation tests may be in order for individual patients.

#### **Dental procedures:**

1. In general terms, most oncology/hematology protocols (exclusive of HCT, which will be discussed later) are divided into phases (cycles) of chemotherapy, in addition to other therapies (e.g., radiotherapy, surgery). The patient's blood counts normally start falling 5 to 7 days after the beginning of each cycle, staying low for approximately 14-21 days, before rising again to normal levels for a few days until the next cycle begins. Ideally, all dental care should be completed before cancer therapy is initiated. When that is not feasible, temporary restorations may be placed and non-acute dental treatment may be delayed until the patient's hematological status is stable.<sup>5,8,10,11</sup>

**2. Prioritizing procedures:** When all dental needs cannot be treated before cancer therapy is initiated, priorities should be infections, extractions, periodontal care (e.g., scaling, prophylaxis), and sources of tissue irritation before the treatment of carious teeth, root canal therapy for permanent teeth, and replacement of faulty restorations.<sup>10</sup> The risk for pulpal infection and pain determine which carious lesions should be treated first.<sup>8</sup> Incipient to small carious lesions may be treated with fluorides and/or sealants until definitive care can be accomplished.<sup>5</sup> It is important for the practitioner to be aware that the signs and symptoms of periodontal disease may be decreased in immunosuppressed patients.<sup>5</sup>

**3. Pulp therapy in primary teeth:** Although there have been no studies to date that address the safety of performing pulp therapy in primary teeth prior to the initiation of chemotherapy and/or radiotherapy, many clinicians choose to provide a more definitive treatment in the form of extraction because pulpal/periapical/furcal infections during immunosuppression periods can have a significant impact on cancer treatment and become life-threatening.<sup>5,8,11</sup> Teeth that already have been treated pulpally and are clinically and radiographically sound present minimal risk.

**4. Endodontic treatment in permanent teeth:** Symptomatic non-vital permanent teeth should receive root canal treatment at least 1 week before initiation of cancer therapy to allow sufficient time to assess treatment success before the chemotherapy.<sup>5,10</sup> If that is not possible, extraction is indicated. Extraction is also the treatment of choice for teeth that cannot be treated by definitive endodontic treatment in a single visit. In that case, the extraction should be followed by antibiotic therapy (penicillin or for penicillin-allergic patients, clindamycin) for about 1 week.<sup>5,10,12</sup> Asymptomatic endodontic needs in permanent teeth may be delayed until the hematological status of the patient is stable.<sup>10,11,20</sup> It is important that the etiology of periapical lesions associated with previously endodontically treated teeth be determined because they can be due to a number of factors including pulpal infections, inflammatory reactions, apical scars, cysts, and malignancy.<sup>8</sup> If a periapical lesion is associated with an endodontically treated tooth and no signs or symptoms of infection are present, there is no need for retreatment or extraction since the radiolucency likely is due to an apical scar.<sup>20</sup>

**5. Orthodontic appliances and space maintainers:** Poorly-fitting appliances can abrade oral mucosa and increase the risk of microbial invasion into deeper tissues.<sup>5</sup> Appliances should be removed if the patient has poor oral hygiene and/or the treatment protocol or HCT conditioning regimen carries a risk for the development of moderate to severe mucositis. Simple appliances (e.g., band and loops, fixed lower lingual arches) that are not irritating to the soft tissues may be left in place in patients who present good oral hygiene.<sup>18</sup> Removable appliances and retainers that fit well may be worn as long as tolerated by the patient who maintains

good oral care.<sup>5,8,21</sup> Patients should be instructed to change appliance soaking solutions daily and routinely clean appliance cases with an antimicrobial solution to prevent contamination and reduce the risk of appliance-associated oral infections.<sup>5</sup> If band removal is not possible, vinyl mouth guards or orthodontic wax should be used to decrease tissue trauma.<sup>8</sup>

**6. Periodontal considerations:** Partially erupted molars can become a source of infection because of pericoronitis. The overlying gingival tissue should be excised if the dentist believes it is a potential risk and if the hematological status permits.<sup>8,10</sup> Patients should have a periodontal assessment and appropriate therapy prior to receiving bisphosphonates as part of cancer treatment.<sup>22,23</sup> If the patient has had bisphosphonates and an invasive periodontal procedure is indicated, risks must be discussed with the patient, parents, and physicians prior to the procedure.

**7. Extractions:** There are no clear recommendations for the use of prophylactic antibiotics for extractions. Recommendations generally have been empiric or based on anecdotal experience. Surgical procedures must be as atraumatic as possible, with no sharp bony edges remaining and satisfactory closure of the wounds.<sup>5,8,10-12</sup> If there is documented infection associated with the tooth, antibiotics— ideally chosen with the benefit of sensitivity testing— should be administered for about 1 week.<sup>5,8,10,12</sup>

- To minimize the risk of development of osteonecrosis or osteoradionecrosis, patients who will receive bisphosphonates or radiation to the jaws as part of the cancer treatment must have all oral surgical procedures completed before those measures are instituted.<sup>22,23</sup> If the patient has received bisphosphonates or radiation to the jaws and an oral surgical procedure is necessary, risks must be discussed with the patient, parents, and physician prior to the procedure.
- Loose primary teeth should be allowed to exfoliate naturally, and the patient should be counseled to not play with them in order to avoid bacteremia. When the patient cannot comply with this recommendation, the teeth should be removed if the hematologic parameters allow.
- Non-restorable teeth, root tips, teeth with periodontal pockets >6 mm, symptomatic impacted teeth, and teeth exhibiting acute infections, significant bone loss, involvement of the furcation, or mobility should be removed ideally 2 weeks (or at least 7 to 10 days) before cancer therapy is initiated to allow adequate healing.<sup>1,5,8,10,11</sup>
- Some practitioners prefer to extract all third molars that are not fully erupted, particularly prior to HCT, while others favor a more conservative approach, recommending extraction of third molars at risk for pulpal infection or those associated with significant periodontal infection, including pericoronitis.<sup>8</sup>

### ***Dental and oral care during immunosuppression periods***

#### ***Objectives***

The objectives of a dental/oral care during cancer therapy are three-fold:

1. to maintain optimal oral health during cancer therapy;
2. to manage any oral side effects that may develop as a consequence of the cancer therapy; and
3. to reinforce the patient and parents' education regarding the importance of optimal oral care in order to minimize oral problems/discomfort during treatment.

#### ***Preventive strategies***

**Oral hygiene:** Intensive oral care is of paramount importance because it reduces the risk of developing moderate/severe mucositis without causing an increase in septicemia and infections in the oral cavity.<sup>1-12</sup> Thrombocytopenia should not be the sole determinant of oral hygiene as patients are able to brush without bleeding at widely different levels of platelet count.<sup>8,9,13</sup> Patients should use a soft nylon brush 2 to 3 times daily and replace it on a regular (every 2-3 months) basis.<sup>8</sup> Fluoridated toothpaste may be used but, if the patient does not tolerate it during periods of mucositis due to oral burning or stinging sensations, it may be discontinued and the patient should brush with water alone. If moderate to severe mucositis develops and the patient cannot tolerate a regular soft nylon toothbrush or an end-tufted brush, foam brushes or super soft brushes soaked in chlorhexidine may be used.<sup>9,17</sup> Otherwise, foam or super soft brushes should be discouraged because they do not allow for effective cleaning.<sup>9,19</sup> The use of a regular brush should be resumed as soon as the mucositis improves.<sup>8</sup> Brushes should be air-dried between uses.<sup>8</sup> Electric or ultrasonic brushes are acceptable if the patient is capable of using them without causing trauma and irritation.<sup>1,8</sup> If patients are skilled at flossing without traumatizing the tissues, it is reasonable to continue flossing throughout treatment.<sup>8</sup> Toothpicks and water irrigation devices should not be used when the patient is pancytopenic to avoid tissue trauma.<sup>8,10</sup>

**Diet:** Dental practitioners should encourage a non-cariogenic diet and advise patients/parents about the high cariogenic potential of dietary supplements rich in carbohydrate and oral pediatric medications rich in sucrose.

**Fluoride:** Preventive measures include the use of fluoridated toothpaste, fluoride supplements if indicated, neutral fluoride gels/rinses, or applications of fluoride varnish for patients at risk for caries and/or xerostomia. A brush-on technique is convenient, familiar, and simple and may increase the likelihood of patient compliance with topical fluoride therapy.<sup>8</sup>

Lip care: Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products.<sup>8,11</sup>

**Education:** Patient/parent education includes reinforcing the importance of optimal oral hygiene and teaching strategies to manage soft tissue changes (e.g., mucositis, oral bleeding, xerostomia) in order to minimize oral problems/discomfort during treatment and the possible acute and long-term effects of the therapy in the craniofacial complex.

### **Dental care**

During immunosuppression, elective dental care must not be provided. If a dental emergency arises, the treatment plan should be discussed with the patient's physician who will make recommendations for supportive medical therapies (e.g., antibiotics, platelet transfusions, analgesia). The patient should be seen every 6 months (or in shorter intervals if there is a risk of xerostomia, caries, trismus, and/or chronic oral GVHD) for an oral health evaluation during treatment, in times of stable hematological status and always after reviewing the medical history. If a central line is still in place and an invasive dental procedure is planned, consultation with the oncologist is recommended.<sup>17</sup>

### **Management of oral conditions related to cancer therapies**

**Mucositis:** Mucositis care remains focused on palliation of symptoms and efforts to reduce the influence of secondary factors on mucositis.<sup>5,10,12</sup> The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology has published guidelines (which are updated regularly) for treatment of mucositis.<sup>24</sup> Studies on the use of chlorhexidine for mucositis have given conflicting results. Most studies have not demonstrated a prophylactic impact, although reduced colonization of candidal species has been shown.<sup>7,12,24</sup> Patient-controlled analgesia has been helpful in relieving pain associated with mucositis, reducing the requirement for oral analgesics. There is no significant evidence of the effectiveness or tolerability of mixtures containing topical anesthetics (e.g., "Philadelphia mouthwash", "magic mouthwash").<sup>24</sup> The use of topical anesthetics often is recommended for pain management although there are no studies available to assess the benefit and potential for toxicity. Lidocaine use may obtund or diminish taste and the gag reflex and/or result in a burning sensation, in addition to possible cardiovascular and CNS effects. Local application may be useful for painful ulcers.<sup>7</sup>

**Oral mucosal infections:** The signs of inflammation and infection may be greatly diminished during neutropenic periods. Thus, the clinical appearance of infections may differ significantly from the normal.<sup>1,10</sup> Close monitoring of the oral cavity allows for timely diagnosis and treatment of fungal, viral, and bacterial infections. Prophylactic nystatin is not effective for the prevention and/or treatment of fungal infections.<sup>5,26</sup> Oral cultures and/or biopsies of all suspicious lesions should be performed and prophylactic medications should be initiated until more specific therapy can be prescribed.<sup>1,5,8-12</sup>

**Oral bleeding:** Oral bleeding occurs due to thrombocytopenia, disturbance of coagulation factors, and/or damaged vascular integrity. Management should consist of local approaches (e.g., pressure packs, antifibrinolytic rinses, gelatin sponges) and systemic measures (e.g., platelet transfusions, aminocaproic acid).<sup>5,6,8,10</sup>

**Dental sensitivity/pain:** Tooth sensitivity could be related to decreased secretion of saliva during radiation therapy and the lowered salivary pH.<sup>5,8,10</sup> Patients who are using plant alkaloid chemotherapeutic agents (e.g., vincristine, vinblastine) may present with deep, constant pain affecting the mandibular molars with greater frequency, in the absence of odontogenic pathology. The pain usually is transient and generally subsides shortly after dose reduction and or cessation of chemotherapy.<sup>5,8,10</sup>

**Xerostomia:** Sugar-free chewing gum, or candy, sucking tablets, special dentifrices for oral dryness, saliva substitutes, frequent sipping of water, alcohol-free oral rinses, and/or oral moisturizers are recommended.<sup>8,27</sup> Placing a humidifier by bedside at night may be useful.<sup>10</sup> Saliva stimulating drugs are not approved for use in children. Fluoride rinses and gels are recommended highly for caries prevention in these patients.

**Trismus:** Daily oral stretching exercises/physical therapy must continue during radiation treatment. Management of trismus may include prosthetic aids to reduce the severity of fibrosis, trigger-point injections, analgesics, muscle relaxants, and other pain management strategies.<sup>3,5,10</sup>

***Dental and oral care after the cancer therapy is completed (exclusive of HCT)*****Objectives**

The objectives of a dental/oral examination after cancer therapy ends are two-fold:

1. to maintain optimal oral health; and
2. to reinforce to the patient/parents the importance of optimal oral and dental care for life.

**Preventive strategies**

**Oral hygiene:** Patients must brush their teeth 2 to 3 times daily with a soft nylon toothbrush. Brushes should be air-dried between uses.<sup>8</sup> Patients should floss daily.

**Diet:** Dental practitioners should encourage a non-cariogenic diet and advise patients/parents about the high cariogenic potential of dietary supplements rich in carbohydrate and oral pediatric medications rich in sucrose.

**Fluoride:** Preventive measures include the use of fluoridated toothpaste, fluoride supplements if indicated, neutral fluoride gels/rinses, or applications of fluoride varnish for patients at risk for caries and/or xerostomia. A brush-on technique is convenient, familiar, and simple and may increase the likelihood of patient compliance with topical fluoride therapy.<sup>8</sup>

**Lip care:** Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products.<sup>8,11</sup>

**Education:** The importance of optimal oral and dental care for life must be reinforced. It is also important to emphasize the need for regular follow-ups with a dental professional, especially for patients who are at risk for or have developed GVHD and/or xerostomia and those less than 6 years of age during treatment due to potential dental developmental problems caused by cancer therapies.

**Dental care**

**Periodic evaluation:** The patient should be seen at least every 6 months (or in shorter intervals if issues such as chronic oral GVHD, xerostomia, or trismus are present). Patients who have experienced moderate or severe mucositis and/or chronic oral GVHD should be followed closely for malignant transformation of their oral mucosa (e.g., oral squamous cell carcinoma).<sup>6,25</sup>

**Orthodontic treatment:** Orthodontic care may start or resume after completion of all therapy and after at least a 2 year disease free survival when the risk of relapse is decreased and the patient is no longer using immunosuppressive drugs.<sup>21</sup> A thorough assessment of any dental developmental disturbances caused by the cancer therapy must be performed before initiating orthodontic treatment.

The following strategies should be considered when providing orthodontic care for patients with dental sequelae:

1. use appliances that minimize the risk of root resorption,
2. use lighter forces,
3. terminate treatment earlier than normal,
4. choose the simplest method for the treatment needs, and
5. do not treat the lower jaw.<sup>28</sup>

However, specific guidelines for orthodontic management, including optimal force and pace, remain undefined. Patients who have used or will be given bisphosphonates in the future present a challenge for orthodontic care. Although bisphosphonate inhibition of tooth movement has been reported in animals, it has not been quantified for any dose or duration of therapy in humans.<sup>29</sup> Consultation with the patient's parents and physician regarding the risks and benefits of orthodontic care in this situation is recommended.

**Oral surgery:** Consultation with an oral surgeon and/or periodontist and the patient's physician is recommended for nonelective oral surgical and invasive periodontal procedures in patients who have used or are using bisphosphonates or those who received radiation therapy to the jaws in order to devise strategies to decrease the risk of osteonecrosis and osteoradionecrosis, respectively. Elective invasive procedures should be avoided in these patients.<sup>28</sup>

**Xerostomia:** Sugar-free chewing gum or candy, special dentifrices for oral dryness, saliva substitutes, frequent sipping of water, alcohol-free oral rinses, and/or oral moisturizers are recommended.<sup>8,27</sup> Placing a humidifier by bedside at night may be useful.<sup>10</sup> Saliva stimulating drugs are not approved for use in children. Fluoride rinses and gels are recommended highly for caries prevention in these patients.

**Trismus:** Daily oral stretching exercises/physical therapy should continue after radiation therapy is finished in order to prevent or ameliorate trismus. Management of trismus may include prosthetic aids to reduce the severity of fibrosis, trigger-point injections, analgesics, muscle-relaxants, and other pain management strategies.<sup>3,5,10</sup>

### ***Hematopoietic cell transplantation***

Specific oral complications can be correlated with phases of HCT.<sup>8,14,15</sup>

#### ***Phase I: Pre-transplantation***

The oral complications are related to the current systemic and oral health, oral manifestations of the underlying condition, and oral complications of recent medical therapy. Most of the principles of dental and oral care before the transplant are similar to those discussed for pediatric cancer.<sup>16</sup> The 2 major differences are:

1. in HCT, the patient receives all the chemotherapy and/or total body irradiation in just a few days before the transplant, and
2. there will be prolonged immunosuppression following the transplant.

Elective dentistry will need to be postponed until immunological recovery has occurred, which may take as long as 9 to 12 months after HCT, or longer if chronic GVHD or other complications are present.<sup>5,8</sup> Therefore, all dental treatment must be completed before the patient becomes immunosuppressed.

#### ***Phase II: Conditioning/neutropenic phase***

In this phase, which encompasses the day the patient is admitted to the hospital to begin the transplant conditioning to 30 days post-HCT, the oral complications are related to the conditioning regimen and supportive medical therapies.<sup>8</sup> Mucositis, xerostomia, oral pain, oral bleeding, opportunistic infections, and taste dysfunction may be seen. The patient should be followed closely to monitor and manage the oral changes and to reinforce the importance of optimal oral care. Dental procedures usually are not allowed in this phase due to the patient's severe immunosuppression.

#### ***Phase III: Initial engraftment to hematopoietic reconstitution***

The intensity and severity of complications begin to decrease normally 3 to 4 weeks after transplantation. Oral fungal infections and herpes simplex virus infection are most notable. Oral GVHD can become a concern for allogeneic graft recipients. A dental /oral examination should be performed and invasive dental procedures, including dental cleanings and soft tissue curettage, should be done only if authorized by the HCT team because of the patient's continued immunosuppression.<sup>8</sup> Patients should be encouraged to optimize oral hygiene and avoid a cariogenic diet. Attention to xerostomia and oral GVHD manifestations is crucial. HCT patients are particularly sensitive to intraoral thermal stimuli between 2 and 4 months post-transplant.<sup>8</sup> The mechanism is not well understood, but the symptoms usually resolve spontaneously within a few months. Topical application of neutral fluoride or desensitizing toothpastes helps reduce the symptoms.<sup>8</sup>

#### ***Phase IV: Immune reconstitution/ late post-transplantation***

After day 100 post-HCT, the oral complications predominantly are related to the chronic toxicity associated with the conditioning regimen, including salivary dysfunction, craniofacial growth abnormalities (especially in patients less than 6 years of age at the time of treatment), late viral infections, oral chronic GVHD, and oral squamous cell carcinoma.<sup>8</sup> Periodic dental examinations with radiographs can be performed, but invasive dental treatment should be avoided in patients with profound impairment of immune function.<sup>8</sup> Consultation with the patient's physician and parents regarding the risks and benefits of orthodontic care is recommended.

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