Oral and General Health - Exploring the Connection

Research Review December 2010

Oral Health of Non-Head & Neck Cancer Patients
Part 1: Oral Manifestations of Non-Head & Neck Cancer
Part 2: Oral Complications from Non-Head & Neck Cancer Therapy: Manifestations, Prevention & Treatment

PROFESSIONAL VERSION

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Part 2: Oral Complications from Non-Head & Neck Cancer Therapy:
Features, Prevention & Treatment

CONTENTS

I. ORAL MANIFESTATIONS OF NON-HEAD & NECK CANCER 1

A. Metastatic Tumors to the Oral Cavity 1

B. Oral Manifestations of Hematologic Malignancy 2
   1) Oral Manifestations of Leukemia 2
   2) Oral Features of Multiple Myeloma 3

C. Paraneoplastic Syndromes 4
   1) Paraneoplastic Pemphigus 4
   2) Recurrent Herpes Zoster  5
   3) Sweet’s Syndrome 5

D. Oral Features of Familial Cancer Syndromes 6
   1) Jaw Osteomas and Gardner’s syndrome (GS)  6
   2) Keratinizing Odontogenic Tumors and Neviod Basal Cell Carcinoma Syndrome  6
   3) Mucosal Neuromas and Multiple Endocrine Neoplasia Syndrome (MEN) III 7
   4) Oral and Cutaneous Papules of Cowden syndrome (CS) 7

II. ORAL COMPLICATIONS FROM NON-HEAD & NECK CANCER THERAPY 8

1. Oral Mucositis 8
   Prevention of Oral Mucositis 10
   a) Standard Dose Chemotherapy 10
   b) High Dose Chemotherapy with or without Total Body Irradiation plus HSCT 10
   c) The Role of Basic Oral Care in the Prevention & Management of Oral Mucositis 11
   Treatment of Oral Mucositis 11

2. Stomatitis and Oral Ulcers; Erythema Multiforme and Stevens-Johnson Syndrome 12

3. Oral Candidiasis 12
   Prevention of Oral Candidiasis 13
   Treatment of Oral Candidiasis 13

4. Reactivation of Herpes Simplex Virus and Oral Bacterial and Viral Infections 13
   a) Reactivation of Oral Herpes Virus Infection 13
   Prevention of Reactivation of HSV 14
   b) Oral Bacterial Infections in the Neutropenic Cancer Patient 14
   Prevention of oral bacterial infection during myelosuppressive chemotherapy 15
   Treatment/Management of Oral Bacterial Infection during myelosuppressive Chemotherapy 16

5. Salivary Gland Hypofunction and Xerostomia 16

6. Dysgeusia and other Taste Disorders 17

7. Oral Graft-versus-Host Disease (GVHD) 18
   Management of Chronic Oral GVHD 20
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ)</td>
<td>21</td>
</tr>
<tr>
<td>Prevention and Treatment of BRONJ</td>
<td>23</td>
</tr>
<tr>
<td>III. 2010 PUBLICATIONS: SPECIAL SYSTEMATIC REVIEWS</td>
<td>25</td>
</tr>
<tr>
<td>IV. CONCLUSION</td>
<td>27</td>
</tr>
<tr>
<td>V. BIBLIOGRAPHY</td>
<td>28</td>
</tr>
<tr>
<td>VI. LIST OF ACRONYMS</td>
<td>35</td>
</tr>
</tbody>
</table>
I. ORAL MANIFESTATIONS OF NON-HEAD & NECK CANCER

The dentist can play an important role in the detection, diagnosis, and management of patients with cancer. Because of their expertise in recognizing normal conditions and pathology of the head and neck, the dental team is uniquely qualified to recognize oral manifestations of cancer and facilitate early diagnosis and treatment. Once a patient has been diagnosed with cancer, the dental team can play a critical role in the prevention, diagnosis, and management of oral complications of cancer therapy. These are the foci of this review: 1) the oral manifestations of non-head and neck cancer and 2) oral complications of treatment of non-head and neck cancer. This report is based on findings from a comprehensive review of the medical and dental literature until August 2010.

A. Metastatic Tumors to the Oral Cavity

There have been several large case series reporting signs and symptoms of cancers that have metastasized to the oral cavity from distant sites (1, 2).

The mandible (75%) is the site most often affected, followed by the maxilla (20%) and both jaws (5%). More than 80% of cases involve the molar region. The most frequent site of the primary tumor for females is breast, followed by adrenal gland, colon/rectum, genital, and thyroid. In males, the most common primary site is the lungs (2), followed by prostate, kidney, colon/rectum, and bronchi. The presenting signs of metastatic cancer were swelling (70%), pain (54%), ulcerations (54%), and bleeding (25%); but 30% of cases are asymptomatic (1). In these two large studies, other symptoms reported included mobility of teeth, paresthesia, trismus, cervical lymphadenopathy, epistaxis, and pathologic fracture (1, 2). In up to a quarter of cases, the oral lesion was the first sign of the malignancy (2). Most metastatic oral lesions were found in patients in their fifth to seventh decade. The mean age for patients with jawbone metastases was lower than soft tissue metastases (2). In women, about 40% of the jawbone lesions were from the breast and in men, about 10% of the jawbone lesions were from the prostate (2).

When lesions involved the jaw and radiographs were available, 86% showed a lytic radiolucent lesion with ill-defined margins; 5% had no radiographic features (2). In this study, once the metastatic lesion was diagnosed, the average survival time was 7 months. Treatments included local resection, radiotherapy or chemotherapy. Often, the goal of therapy was not cure, but simply to improve quality of life since the disease was so advanced at the time of diagnosis (2).
B. Oral Manifestations of Hematologic Malignancy

B1) Oral Manifestations of Leukemia:

*Acute lymphocytic leukemia (ALL)* is a cancer of white blood cells. Typical clinical signs of symptoms of ALL include infection, fatigue, pallor, uncontrolled or spontaneous bleeding, hepatomegaly, splenomegaly, and lymphadenopathy. The majority of patients have B-cell ALL. This affects young children with a peak incidence at 4 years of age. T-cell ALL is less common and tends to affect adolescents. NK-cell ALL is seen more often in adults (NK-cell=Natural Killer cell, a type of cytotoxic lymphocyte). The most common oral manifestation of ALL is spontaneous gingival bleeding. This tends to occur more often when platelet counts are < 20,000 mm$^3$. Because these patients are immunosuppressed, they may also present with oral candidiasis, neutropenic ulcers of the oral mucosa -- which can resemble aphthous ulcers but without the erythema -- herpetic infections that are not limited to the keratinized mucosa. Gingival hypertrophy and inflammation as well as leukemic infiltration into the gingival and other localized oral mucosal sites are possible. Numb chin syndrome has also been associated with ALL. The prognosis of ALL is generally good; in children, the cure rate is 85%. In adults, the cure rate is about 50%. Some variants have a worse prognosis. Treatment usually consists of multiple chemotherapeutic drugs. Those who fail this chemotherapy may be treated with hematopoietic stem cell transplantation (HSCT). ALL may be suspected based on clinical features and abnormal CBC, but diagnosis is made by bone marrow biopsy.

Chronic lymphocytic leukemia is the most common form of leukemia and affects mainly older adults; however it can be seen in early middle age. 95% are B-cell chronic lymphocytic leukemia (B-CLL), also known as chronic lymphoid leukemia (CLL). It may be detected as an incidental finding by routine CBC/differential or can present as enlarged lymph nodes. Some patients may have symptoms such as fever, night sweats, unintentional weight loss, fatigue, frequent infections, bleeding, and lymphadenopathy. Diagnosis is made from blood smear and bone marrow biopsy. CLL is often associated with autoimmune complications, including hemolytic anemia, autoimmune thrombocytopenia, and hypogammaglobulinemia. The oral manifestations of CLL are very similar to ALL. Paraneoplastic pemphigus has been associated with CLL (3). The prognosis and treatment of CLL is variable and depends on staging. Treatment may include various multidrug chemotherapeutic regimens; HSCT is also an option for some. Occasionally, radiation therapy may be used to treat splenic involvement.

Acute myelogenous leukemia (AML) is more common in men than in women. Its incidence is 2.3/100,000 people. The incidence increases with age and is associated with several genetic disorders, environmental exposure to teratogens, drugs, and radiation. The most common symptoms
are fatigue, weight loss, and anorexia. Bleeding problems are very common. Patients may also present with hepatomegaly, splenomegaly, and infection. Mucosal bleeding is a striking feature of this disease and can occur in the mouth. Diagnosis is made on the basis of clinical features, complete blood count (CBC), blood smear, and bone marrow biopsy. There are several different subtypes of AML, based on specific genetic mutation, cellular morphology, and immunotyping. The oral manifestations of AML are more common in some subtypes and include chloroma (granulocytic sarcoma) and opportunistic infections. Leukemic infiltration into the gingiva and other soft tissues -- including the tongue, which can present as diffuse enlargement of the tongue -- is also frequently seen. Gingival bleeding is very common in AML. Sweet’s syndrome can be associated with AML, manifesting as recurrent oral ulcers as described above (4). AML is treated according to type and stage with multiple chemotherapeutic drugs. Only 20% of patients with AML treated with standard therapy achieve long-term survival without disease (4).

Chronic myelogenous leukemia (CML), a disease of older adults, is often asymptomatic and found incidentally on routine blood work. However, those with symptoms usually complain of fatigue, anorexia, or weight loss. CML has three stages. At first, it presents as a chronic mild disease, which typically lasts for 5 to 6 years. Over time, CML progresses to blast crisis, which manifests as acute leukemia and typically is associated with rapid deterioration and death. The oral manifestations of CML include petechiae, mucosal bleeding, and acute periodontitis. Oral candidiasis is a common opportunistic infection in CML. CML is treated with chemotherapy including interferon-alpha, hydroxyurea and busulfan. However, in recent years, Gleevec (imatinib mesylate) has largely replaced these conventional agents. HSCT can be highly successful in treating CML with cure rates as high as 85% (4).

B2) Oral Features of Multiple Myeloma:

Multiple myeloma (MM), a hematologic malignancy of older adults, is characterized by monoclonal proliferation of abnormal plasma cells. There are approximately 15,000 new case of MM every year in the US. The median age at diagnosis is 65 years, and it affects men more than women. It has been associated with environmental exposure to teratogens, such as radiation and pesticides, but the cause is still unknown. MM is diagnosed on the basis of blood tests and urinalysis that detect elevated monoclonal immunoglobulins, radiographic examinations, and bone marrow biopsy. MM is treated with a combination of intravenous bisphosphonate drugs (pamidronate, zoledronate), corticosteroids (dexamethasone, prednisone) and cytotoxic chemotherapeutic agents (doxorubicin, vincristine), and/or thalidomide or lenalidomide. Proteasome inhibitors, such as bortezomib (Velcade), are newer
agents used to treat MM. Median survival for patients with MM is about 4 years. HSCT is also used to treat MM with improved survival reported (5).
The oral manifestations of multiple myeloma (MM) can be the first sign of the disease. They can present as toothache, tooth mobility and migration, jaw/facial pain, mucosal ulceration, soft tissue swelling, paresthesia due to nerve compression, and gingival bleeding (6-9).
Radiographic evidence of MM includes multiple punched-out radiolucencies in the jawbones or generalized rarefaction of the bone, a result of osteoporosis from marrow replacement with the malignant cells. The radiographic features in the jaws usually occur later in the disease. Root resorption (10) and periodontal destruction have been reported as well (6).
If the dentist suspects the patient has leukemia or other hematologic malignancy, prompt referral to a pediatrician, internist, or oncologist is indicated. Surgical treatment of dental disease should be coordinated with the patient’s oncologist with careful attention to anemia, thrombocytopenia, and neutropenia and correction if possible prior to surgical procedures to avoid bleeding and infection complications (4, 5).

C. Paraneoplastic Syndromes:
Paraneoplastic syndromes are clinical manifestations of indirect, remote effects of underlying malignancies and their tumor metabolites. Because the severity and progression of these diseases often mimic the clinical course of the underlying malignancy, they can help detect an undiagnosed cancer, and can be monitored as a marker of the cancer progression and response to therapy. The following examples of paraneoplastic syndromes that can present as oral ulcers (11) will be mentioned: 1) paraneoplastic pemphigus, 2) recurrent Herpes zoster, and 3) Sweet syndrome.

C1) Paraneoplastic Pemphigus:
Paraneoplastic pemphigus (PNP) is a rare autoimmune vesiculobullous disease of the skin and mucous membranes that often presents initially as severe oral ulcers. It is typically associated with non-Hodgkin’s lymphoma and lymphocytic leukemia (3, 4, 12). Less commonly it has been associated with carcinomas, sarcomas and thymomas (11). The mean age of patients with PNP is 60 years and it affects males and females equally. In the mouth, PNP appears as diffuse, persistent, painful oral ulcers and collapsed blisters on the buccal mucosa and vermilion of the lips, mimicking oral erythema multiforme or Stevens-Johnson syndrome (13, 14). The skin lesions consist of an itchy papulosquamous eruption that may mimic lichen planus; eventually fragile blisters develop that easily rupture leaving broad open erosions. These lesions can involve the palms and soles, which is unusual for pemphigus vulgaris. 70% of patients also develop a pseudomembranous conjunctivitis
which can lead to scarring, very similar to cicatricial pemphigoid. The diagnosis of PNP is made on the basis of clinical features, and biopsy and direct immunofluorescence studies of peri-lesional mucosa or skin. PNP has a poor prognosis and mortality approaches 90%. If the dentist suspects a patient has oral ulcers of PNP, the patient’s physician should be contacted with the suspicion; a dermatologist with experience treating vesiculobullous diseases should be consulted for diagnosis and treatment. If there has been no primary cancer diagnosis, then referral to an oncologist is indicated. Treatment includes immunosuppressive therapy such as prednisone combined with steroid sparing agents (3, 11).

C2) Recurrent Herpes Zoster:
Recurrent Herpes zoster (HVZ) (shingles) is an infection caused by the Herpes varicella zoster virus, common in elderly and immunosuppressed patients. It can be a sign of an underlying malignancy, typically Hodgkin’s or non-Hodgkin’s lymphoma. It is also seen in patients with cancer who have undergone treatment with radiation, chemotherapy or HSCT. Most patients who present with severe disseminated painful HVZ have an underlying neoplasm. In the head and neck, the lesions typically follow the distribution of the trigeminal nerve in a unilateral fashion, with a sharp border at the midline. When the second and third divisions are involved, both cutaneous and oral mucosal sites are affected. The lesions start as blisters, and once they rupture, shallow irregular ulcers arise on the both keratinized and non-keratinized oral mucosa. The skin lesions appear as blisters, pustules, crusted hemorrhagic blisters and ulcers. Rare oral complications of oral HVZ include neuralgia, osteonecrosis, and exfoliation and devitalization of teeth (11, 15-17). Treatment of recurrent HVZ consists of antiviral medications: acyclovir, valacyclovir, and famciclovir are effective when taken within 48 hours of lesion onset (11).

C3) Sweet’s Syndrome:
Sweet’s syndrome (SS) is also known as acute febrile neutrophilic dermatosis. It is rare and only 10-20% of cases are associated with an underlying malignancy, most often a hematologic malignancy. SS tends to occur in young patients and those in the fourth to sixth decades. The oral lesions resemble aphthous ulcers without an erythematous halo. The skin lesions are tender violaceous or erythematous plaques and nodules that appear suddenly, usually on the face, neck, and extremities. Sometimes there are blisters. SS is diagnosed by skin biopsy. Treatment consists of systemic corticosteroids, anti-inflammatory drugs, and steroid-sparing agents. Relapses are common in cases associated with malignancy (11).
D. Oral Features of Familial Cancer Syndromes

The familial cancer syndromes are genetic disorders associated with increased risk of internal malignancies. Several of them have orofacial manifestations. The dentist can contribute to the early diagnosis and treatment of such patients by recognizing these orofacial markers of internal malignancy. The more common of these disorders are summarized here.

D1) Jaw Osteomas and Gardner’s syndrome (GS):

Gardner’s syndrome (GS) is an autosomal dominant disorder associated with mutations in the adenomatosis polyposis coli gene (APC). GS is characterized by premalignant gastrointestinal polyps, colorectal cancer, osteomas, and cutaneous ocular and soft tissue lesions. 80% of patients with Gardner’s syndrome have osteomas. The occurrence of 3 or more jaw osteomas is highly suggestive of this disorder and should prompt referral to a gastroenterologist for assessment and diagnosis. The osteomas often precede the other manifestations, especially when they arise in puberty. Supernumerary and impacted teeth are also associated with GS. The osteomas of GS are benign. Large ones may require surgical removal. Patients who present with multiple osteomas should be referred for gastrointestinal work-up and genetic testing for the APC mutations associated with this disorder. Patients with GS require regular colonoscopy, upper endoscopy, and in some cases, prophylactic colostomy (11).

D2) Keratinizing Odontogenic Tumors (KOT) & Nevoid Basal Cell Carcinoma Syndrome (NBCCS):

Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant condition associated with multiple keratinizing odontogenic tumors (KOTs); basal cell carcinomas, medulloblastomas, and other neoplasms; bifid ribs and other skeletal anomalies; and characteristic facial features. KOT’s are benign but aggressive cystic neoplasms that appear as well-defined unilocular or multilocular radiolucencies within the jaws, with a predilection for the mandible. Secondary features include pain and swelling in some patients. KOTs are characterized by a high recurrence rate, especially in syndromic patients. The presence of multiple KOTs should raise a strong suspicion for the syndrome. The features of this syndrome tend to become recognizable in the first and second decades of life. KOTs may be the first manifestation identified by a health care provider. Therefore, dentists can play an important role in early detection of the KOT and the diagnosis of this syndrome. Suspected cases should be referred to an oral and maxillofacial surgeon for biopsy and surgical treatment and genetic assessment and testing for the mutation in the PTCH gene associated with this condition. This gene suppresses tumors if not mutated. Lifelong surveillance by a dermatologist and dentist/oral and maxillofacial surgeon is necessary as the basal cell carcinomas and KOTs continue
to develop throughout life. Prognosis is generally good, but the treatment of the skin and jaw lesions can cause cosmetic deficits (11).

D3) Mucosal Neuromas and Multiple Endocrine Neoplasia Syndromes (MEN) III:

*Multiple endocrine neoplasia syndrome III (MEN III)* is an autosomal dominant disease associated with multiple mucosal neuromas, medullary thyroid carcinoma (MTC) (90%), and pheochromocytoma (50%), a rare tumor of the adrenal gland. Hyperparathyroidism can also be seen with this disorder. Additional secondary features of MEN III disease include joint laxity and long limbs (Marfanoid habitus), diastema, everted eyelids, and protuberant lips. Other neoplasms seen in MEN III include ganglioneuromas of the gastrointestinal tract and tumors of the genitourinary tract. In 95% of patients with MEN III it is caused by a mutation on the *Rearranged during Transfection* (*RET*) gene. Mucosal neuromas often are the first sign of this disease. They can present as small, painless, pedunculated nodules on any mucosal surface, but are most often found on the tongue, lips and labial commissures. The patient should have these lesions biopsied; once confirmed as mucosal neuromas, the patient should be referred for genetic evaluation and testing for the *RET* mutation, as well as for extensive thyroid, adrenal and gynecologic evaluation and treatment. Because MTC is so common and carries such a poor prognosis in this syndrome, prophylactic thyroidectomy is usually performed (11).

D4) Oral and Cutaneous Papules of Cowden Syndrome (CS):

*Cowden syndrome (CS)* is also known as *multiple hamartoma syndrome*. It is an autosomal dominant condition; 95% are associated with a mutation in the phosphatase and tensin homolog (PTEN) gene. CS is characterized by multiple mucocutaneous fibrous papules and increased risk of benign and malignant tumors. 75% of females with CS have breast disease; 30-50% develop breast cancer and in 25% it is bilateral. The breast cancer of CS has a poor prognosis. Men with CS are also at higher risk of developing breast cancer. Thyroid tumors are seen in 40-60% of patients with CS. Tumors of other systems are also very common. 80-90% of patients with CS have oral papules. The oral papules in CS are smooth or verrucoid nodules on the gingiva, tongue, palate, and labial and buccal mucosa. The buccal mucosa may have a cobblestone appearance because of multiple papules. Fissured tongue and high arched palate are other oral manifestations of CS. Cutaneous papules can be found on the skin of the head and neck, appearing as dome-shaped lesions with verrucous surfaces. CS is also associated with keratosis of the palms and soles, skin carcinomas and benign connective tissue neoplasms (11).
II. ORAL COMPLICATIONS FROM NON-HEAD & NECK CANCER THERAPY: FEATURES, PREVENTION & TREATMENT

*Cytotoxic chemotherapy regimens* for non head-and-neck malignancies usually cause transient bone marrow suppression and subsequently increase systemic risk for infection and bleeding. Mucositis of the gastrointestinal mucosa is another significant dose-limiting toxicity of current cytotoxic chemotherapeutic regimens. It causes pain and dysfunction and increases the patient’s risk for local and systemic infection. Therefore, the oral complications of cytotoxic chemotherapy include viral, fungal, and bacterial infections, oral mucositis, dysgeusia and other taste disorders and xerostomia.

*Hematologic malignancies* may be treated with allogeneic or autologous bone marrow transplants. Patients receiving this type of treatment are at risk for oral complications secondary to their conditioning regimen prior to transplantation and due to immunosuppressive medications or graft versus host disease (GVHD) after transplantation. Conditioning regimens are commonly associated with oral mucositis, and while the bone marrow is suppressed, the risk for oral infection is high.

Chronic GVHD of the oral mucosa is a late complication of bone marrow transplantation and manifests as oral lichenoid lesions which can be very painful. GVHD involvement of the salivary glands leads to xerostomia and its secondary complications.

*Osteonecrosis of the jaw* is a chronic oral complication of intravenous bisphosphonates given to patients for prevention or treatment of skeletal complications of cancer. Patients with metastatic breast and prostate cancer or multiple myeloma who have received intravenous high potency bisphosphonates such as zolendronic acid appear to be at the greatest risk of this potentially serious complication.

This review will discuss the features, prevention, and management of each of these oral complications of cancer therapy.

1. Oral Mucositis

*Oral mucositis* is an important common acute short-term complication of systemic cytotoxic chemotherapy. It is a dose-limiting toxicity of these therapies characterized by ulceration in the oro-esophageal and gastrointestinal mucosa, resulting in significant pain and dysphagia (18).

Furthermore, the combination of oral mucositis and myelosuppression seen with many chemotherapeutic regimens puts the cancer patient at even greater risk of bacteremia and sepsis from oral microbes (19).

Clinically, oral mucositis initially presents as erythema, at about 4-5 days following chemotherapy infusion. The patient often complains of oral burning or intolerance to spicy food. As the mucositis
progresses, at about 7-10 days after chemotherapy ulcers develop. This necessitates opioid
administration for pain management and significant dietary alterations, including the need for total
parenteral nutrition (TPN). With chemotherapy, lesions are usually seen on the movable mucosa of
the buccal mucosa and the lateral and ventral surfaces of the tongue. Chemotherapy-induced
mucositis usually lasts about 1 week and heals by 21 days after infusion.
The mTOR inhibitors (mammalian target of rapamycin) are new anticancer drugs used to treat
advanced renal cancer, and with potential use against advanced breast cancer, lymphoma and
sarcomas. These drugs include temsirolimus, deforolimus, and everolimus. The oral mucositis
associated with these drugs is quite different from the usual chemotherapy-induced mucositis
because of its rapid onset (usually within 5 days) and mild to moderate severity (grade 1-2).
Common locations include the labial mucosa, lateral tongue, buccal mucosa and soft palate (all non-
eratinized surfaces). The oral ulcers look like aphthous ulcers, and lack the typical
pseudomembrane associated with chemotherapy-induced mucositis. The mucositis and oral ulcers
associated with mTOR inhibitors usually resolve on its own or after withholding treatment (20).
Mucositis has significant health and economic impact on cancer patients. For example, stem cell
recipients with mucositis have been shown to have more days of fever, antibiotic use, opioid use and
TPN than patients without mucositis, and length of hospital stay is increased with its concomitant
costs. Mucositis also has an indirect effect on treatment outcomes as it is one of the most common
reasons for break in radiation treatment or dose reduction of chemotherapy (21).
The prevalence of mucositis varies with treatment regimen. It is seen in over 50% of patients treated
with flurouracil, adriamycin and cytoxan (FAC) for node-positive breast cancer; it has been reported
as affecting 15-20% of patients being treated for colorectal cancer. Other high risk groups are
patients receiving conditioning regimens for stem cell transplant that include total body irradiation or
high dose melphalan, and patients receiving specific induction protocols for acute leukemia (21).
Chemotherapy-induced mucositis risk and severity are agent and dose-dependent. The most toxic
agents include 5-fluorouracil (5-FU), cisplatin, etoposide and melphalan (22, 23). Mucositis is also
common with regimens using doxorubicin, vinblastine, taxanes, and methotrexate, but is uncommon
with asparginase and carmustine (24). Combination therapy is associated with higher risk for
mucositis.
Diagnosis of oral mucositis is based on the clinical appearance and timing of the presentation of the
lesions and the knowledge of the specific cancer therapy the patient has received. The differential
diagnosis includes oral viral infections and graft vs. host disease (GVHD). Oral viral infections
differ from oral mucositis in that they usually appear as crops of shallow blisters that ulcerate and
coalesce, are localized, and involve the keratinized mucosa of the hard palate, gingivae, and tongue
dorsum. Fever often accompanies the onset of oral viral lesions. Culture or exfoliative cytology at
the time presentation can be extremely helpful in making the diagnosis and is recommended. GVHD
is only seen in patients who have received allogeneic HSCT and develops following hematologic
recovery, more than 21 days post-transplant. The oral lesions of GVHD are often widespread and
lichenoid in appearance. Xerostomia may accompany these lesions as well, indicating salivary gland
involvement in this disease process. Chemotherapy induced neutropenia may present as necrotizing
gingivitis and should also be considered in the differential diagnosis of oral mucositis (25).
Prevention and palliative care of oral mucositis is primarily the responsibility of nursing, medical
oncology or oral oncology; however the general dentist can provide basic oral care that can help to
reduce the severity of mucositis. In 1998, The Multinational Association of Supportive Care in
Cancer and the International Society for Oral Oncology (MASCC/ISOO) created the Mucositis
Study Section to address important issues in mucositis treatment and research, and in 2000 they
developed evidence-based guidelines for the prevention and treatment of mucositis. The
multidisciplinary panel reviewed and evaluated the scientific literature (18). These guidelines were
recently updated by Keefe et al. (26). Their evidence-based recommendations for prevention and
treatment of mucositis are summarized below:

**Prevention of Oral Mucositis:**

*a. Standard Dose Chemotherapy*

Patients receiving bolus 5-FU chemotherapy should undergo 30 minutes of oral cryotherapy (ice
chips) to prevent oral mucositis. This may also be used for patients treated with bolus doses of
edatrexate. This is administered as ice chips that the patient holds in the mouth during infusion of the
chemotherapy (27, 28). Acyclovir and its analogues should not be used routinely to treat oral
mucositis.

*b. High Dose Chemotherapy with or without Total Body Irradiation plus HSCT*

Keratinocyte growth factor-1 (palifermin) should be used in a dose of 60 mg/kg per day for 3 days
prior to conditioning treatment and for 3 days post-transplantation for the prevention of oral
mucositis. Palifermin is a recombinant human keratinocyte growth factor (KGF). KGF is a member
of the fibroblast growth factor family and is produced by mesenchymal cells. It binds to the
keratinocyte growth factor receptor resulting in differentiation and maturation of epithelial cells.
Palifermin has been shown to bind to endogenous KGF receptors on tongue, buccal mucosa and
esophagus and stimulate epithelial cell proliferation, differentiation and migration. Although there is
some evidence that reactivation of Herpes simplex virus contribute to the severity of mucositis in
some seropositive patients during head and neck radiation, administration of palifermin before and after chemotherapy and/or radiation therapy leads to an increase in epithelial thickness as well as up-regulation of detoxifying enzymes that protect against free radical damage. The most common adverse effects associated with palifermin are skin and mucous membrane reactions, taste alteration, tongue discoloration and oral/perioral dysesthesia (29). Cryotherapy may be used in patients receiving high dose melphalan. This is administered as ice chips that the patient holds in the mouth during infusion of the chemotherapy (27, 28). Low level laser therapy (LLLT) may reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT at treatment centers that are able to support its use. A recent phase III double blind randomized placebo controlled trial showed that the application of daily low level laser therapy at a wavelength of 650nm, and energy density of 2 J/cm², starting the first day of conditioning and continuing through day +2 post -HSCT reduced the severity of oral mucositis and pain scores. There were no adverse effects reported and the procedure was generally well tolerated. Additional research on larger scale is indicated to determine the efficacy and optimal delivery parameters of this therapy in preventing oral mucositis; however these preliminary results are very promising (30).

c. The Role of Basic Oral Care in the Prevention and Management of Oral Mucositis

There is insufficient evidence to provide a guideline for basic oral care, but it is recognized that maintenance of mucosal health, integrity and function is beneficial. Basic oral hygiene and care reduce the impact of oral microbial flora, and prevent soft tissue infections that may have systemic sequelae (26). A good oral hygiene program also prevents caries and gingivitis and their sequelae. Oral care protocols that include patient education may help to reduce the severity of oral mucositis.

Treatment of Oral Mucositis:
Various topical preparations have been used to treat mucositis, including viscous lidocaine, benzocaine, milk of magnesia, kaolin, pectin, sucralfate, chlorhexidine and diphenhydramine, benzydamine (31), glutamine (32) and morphine (33). There is inadequate evidence of efficacy for any of these treatments. There are also concerns about the potential for absorption of lidocaine through damaged oral mucosa, which could lead to toxicity. More research is needed about the toxicity and efficacy of palliative mixtures and individual agents. Simple bland mouth rinses of ½ tsp salt and ½ tsp baking soda in warm water can be soothing to a sore mouth and help in oral hygiene. The patient can use this 4 times per day to help keep the mouth clean and moist. There are also newer bland mouth rinses/coating agents such as Gelclair (Helsinn
Healthcare SA; Lugano, Switzerland) which, in small preliminary trials show some efficacy in reducing the pain associated with mucositis (34, 35).

Mucositis is associated with significant pain; therefore analgesia is a high priority. A Cochrane systematic review (36) concluded that there was no evidence that patient controlled analgesic (PCA) is better than continuous infusion for controlling pain, but less opiate was used per hour and duration of pain was shorter for PCA. Additional well-designed studies are indicated in this important area.

**In summary, the dentist caring for a patient on chemotherapy can help his/her patient by being aware of these oral mucositis recommendations, and providing basic oral care consisting of patient education, disease control, and oral hygiene instruction. These measures can decrease the microbial load in the oral cavity and prevent other complications associated with therapy. Measures specifically designed to prevent and treat oral mucositis can be provided by the patient’s oncology team.**

2. **Stomatitis and Oral Ulcers; Erythema Multiforme and Stevens-Johnson Syndrome**

Stevens-Johnson syndrome (SJS) is a severe life-threatening condition characterized by severe oral mucosa and labial ulcerations, and blistering of the skin. It is considered an adverse drug reaction. The mortality rate of SJS is ~ 30%. SJS usually develop 9-60 days after initiation of the offending drug. Several cases of SJS have been reported in patients with cancer receiving therapy. It has been associated with the concurrent use of Gleevec (imatinib) and allopurinol for CML (14), lenalidomide and dexamethasone for multiple myeloma (13) after radiotherapy for breast cancer (37) and after HSCT and concomitant infection with *Mycoplasma pneumoniae* (38). SJS is a life-threatening condition; suspected cases should be referred immediately to a hospital for admission and supportive therapy.

3. **Oral Candidiasis**

Oropharyngeal candidiasis (OPC) is a fungal infection on the mucous membranes of the mouth and pharynx. It is a common infection during myelosuppression from chemotherapy or chronic graft versus host disease (GVHD) as well. Infection with Candida can be painful and can lead to significant morbidity. Systemic spread of Candida via the blood stream (candidemia) presents a potentially life-threatening condition and is usually confined to severely immunocompromised individuals, such as cancer patients under treatment. Candida albicans is the most common organism isolated in OPC. However, recent evidence indicates the emergence of non-albicans yeast in OPC (39, 40). These other species include C. dublensis, C. glabrata, and C. krusei (41).
Prevention of Oral Candidiasis:
Cochrane systematic reviews of the literature on interventions for preventing oral Candidiasis for patients receiving cancer treatment (42-44) showed strong evidence that drugs absorbed or partially absorbed from the GI tract (fluconazole, itraconazole, ketoconazole) prevented OPC in this patient population. The data also suggested these drugs prevented OPC better than those that were not absorbed (miconazole and clotrimazole) from the GI tract (39, 42-44).

Treatment of Oral Candidiasis:
Many different agents have been used to treat OPC. Clotrimazole has been shown to be more effective than nystatin for treatment of OPC; clotrimazole 10 mg troches administered five times per day is effective in treating mild to moderate OPC (45). Some topical preparations have a high sucrose content, which may contribute to caries risk in the xerostomic patient. Fluconazole 50-100 mg daily has been associated with clinical recovery in 80 % of patients within 10 days, or within 5 days with 200 mg daily. Clotrimazole at 50mg was more effective than at the lower dose of 10 mg in eradicating oral Candidiasis (50). Complete mycologic cure is difficult to achieve. Resistance to fluconazole is associated with non-albicans yeast, such as Candida glabrata and Candida krusei (46). A recently updated Cochrane systematic review of this topic failed to find evidence sufficiently strong to support one drug over another in the treatment of OPC in this population (47-50).

In summary, oropharyngeal candidiasis is a common complication of cancer and its treatment. Although initially encountered at diagnosis or during treatment of cancer, it also can present a long-term problem in patients with xerostomia. Antifungal prophylaxis may be beneficial in high-risk patients; the oncology team should make this decision. Several agents treat OPC, including topical medications, such as clotrimazole, and systemic agents, such as fluconazole and ketoconazole. The authors of the Cochrane review on this topic updated in 2010 conclude “There is insufficient evidence to claim or refute a benefit for any antifungal agent in treating candidiasis. Further well-designed, placebo-controlled trials ....... are needed. Clinicians need to make a decision on whether to prevent or treat oral Candidiasis in patients receiving treatment for cancer.” (50)

4. Reactivation of Herpes Simplex Virus and Oral Bacterial and Viral Infections
Patients undergoing cancer therapy are susceptible to a variety of opportunistic infections as a consequence of mucosal injury and myelosuppression (51). Untreated dental infection also poses a significant risk for systemic infection and sepsis during periods of neutropenia. This section
addresses the problems of oral bacterial infections and viral infections, specifically reactivation of latent Herpes virus infections, including Herpes Simplex (HSV) and cytomegalovirus (CMV).

4a) Reactivation of Oral Herpes Virus Infection:
Seropositive individuals planned to receive cytotoxic chemotherapy or HSCT are at risk for reactivation of Herpes viruses during treatment. Herpes simplex is the most common of these. These lesions can affect any mucosal surface, and recrudescent lesions may develop. In general, the risk for reactivation correlates with the dose intensity of the antineoplastic therapy. Reactivation occurs in up to 70-80% of seropositive HSCT and acute leukemia patients, and in 38-60% of non-Hodgkin’s lymphoma patients under treatment (51). Deep and extensive oral ulcerations may be the presenting feature. The infection may spread contiguously along the mucosal surface, resulting in esophagitis, tracheitis or pneumonitis. Lesions may become persistent, and are usually very painful. Diagnosis is supported by cytologic examination and viral culture of blister contents, if present, or ulcerated lesions. Oral cytomegalovirus associated infection of the lip, labial mucosa, tongue and pharynx has rarely been described in immunocompromised patients and can cause oral mucositis and ulcerations (52).

Prevention of Reactivation of HSV:
Seropositive patients who are immunocompromised routinely receive acyclovir for prophylaxis of HSV infection, extending treatment until resolution of neutropenia. Although oral acyclovir is well tolerated, its half–life is short (2-3 hours) and its low oral bioavailability, necessitates dosing 3-5 times per day. For a patient already suffering from mucositis, nausea and vomiting, this frequent dosing can be problematic. Valacyclovir has a three to five-fold greater bioavailability that oral acyclovir, and can be administered once or twice daily. In a recent clinical trial comparing these two drugs, prophylactic treatment of valacyclovir given either 250 mg twice daily or 500 mg twice daily was comparable to that of acyclovir 400 mg given three times daily for prevention of reactivation of HSV in the oncology setting (53). This has been supported by more recent studies in the HSCT population (54).

4b) Oral Bacterial Infections in the Neutropenic Cancer Patient:
Bacteremia from gram-negative rods has been the most problematic infection in chemotherapy-induced neutropenia. The GI tract is the major source of bacteria in patients who develop mucosal injury during chemotherapy (55). Furthermore, 25-50% of cases of septicemia in neutropenic cancer patients appear to be due to oral organisms (56). In addition, there has been an increase in
bloodstream anaerobic infections seen in neutropenic patients, and most of these patients were found to have oral mucositis or periodontal disease (57). In neutropenic patients, fever usually signals infection. An oral or dental cause may be sought if the source is not readily identifiable. It is important to remember that in neutropenic cancer patients, periodontal or periapical infections may be overlooked because the usual signs of inflammation may be absent. On the other hand, in the presence of mucositis due to chemotherapy, redness and swelling associated with periodontal infection may be mistakenly attributed to the mucositis. Additionally, in patients with severe periodontitis where the infection involves deeper structures, clinical inspection alone may not reveal the problem. Evidence also suggests that subgingival microorganisms and cytokines from the periodontal pocket translocate into the oral cavity and contribute to oral mucositis (58). In about 40 percent of neutropenic cases, the cause of fever is unidentified (59). Pre-existing periodontal disease may induce fever and microbes may spread systemically (60-62). This is supported by the work of Laine and colleagues (63) who found that among patients who received chemotherapy for treatment of lymphoma, those with severe periodontitis experienced more febrile episodes than those with healthy periodontium. Microbes isolated from peripheral blood during febrile neutropenia were similar to those cultured from subgingival plaque of periodontally diseased teeth. Interestingly, these organisms could not be isolated from any other body site, nor were there signs of active inflammation in patients with severe periodontal disease. Patients with periodontal disease undergoing high-dose chemotherapy may develop acute exacerbations in pre-existing sites of disease during episodes of neutropenia (62, 64-67).

**Prevention of Oral Bacterial Infection During Myelosuppressive Chemotherapy:**

Oral care conducted before and during medical therapy reduces oral complications while preventing increase in fever or bacteremia risks (58, 60, 61, 68, 69). Pre-treatment dental management not only reduces oral complications, but also may reduce the length of a patient’s hospital stay (70). Patients scheduled to receive myelosuppressive chemotherapy should undergo a comprehensive dental management program that treats the patient before, during, and after therapy. Before chemotherapy begins, oral and periodontal assessments should be performed, along with treatment of pre-existing infections and preventive treatment of acute complications associated with medical therapy. Pocket depths and loss of attachment should be measured using periodontal probing and radiographs (59).
Treatment/Management of Oral Bacterial Infection During Myelosuppressive Chemotherapy:
Chlorhexidine, which helps reduce plaque formation and disperse established plaque, may assist in managing gingivitis and periodontal involvement. This antimicrobial agent also helps reduce caries risk, and may decrease oral colonization by Candida, as well as aerobic and anaerobic bacteria (71). During chemotherapy, a sound program of oral hygiene should be continually maintained to prevent accumulation of dental plaque that can lead to gingival inflammation and periodontal infection. This may reduce the severity of mucositis during treatment and reduce the potential for septicemia from periodontal sources. In patients with solid tumors, chemotherapy may produce short-term leukopenia, with recovery prior to the next course of chemotherapy, if there are several weeks between rounds of chemotherapy. Dental and periodontal treatment should be provided when the white counts are not suppressed. Antibiotic therapy may be considered when the neutrophil counts are < 500 cells/ml, if the treatment cannot be delayed until the counts are higher than 1000 cells/ml. If necessary, a delay in myelosuppressive therapy should be considered in order to manage a symptomatic dental infection. If asymptomatic periapical pathosis is present, dental treatment may be completed after chemotherapy, and the patient should receive appropriate systemic antibiotics during myelosuppression (66, 72, 73). Elimination of local irritants such as calculus and rough restorations should be planned. Dentures should be cleaned regularly and removed at night (74).

In summary, patients at risk for neutropenia should receive dental and periodontal treatment before chemotherapy begins. Elimination of active and potential dental infections before therapy, and maintenance of good oral hygiene during treatment can reduce the risk of infection and fever associated with oral conditions in patients undergoing myelosuppressive chemotherapy (58-61, 66, 75).

5. Salivary Gland Hypofunction and Xerostomia
Xerostomia is a common oral complication of cancer therapy. It has been reported as a side effect of many drugs used to treat cancer and can occur as a result of the disease itself. Furthermore, it is a common complication of graft versus host disease (GVHD) following allogeneic HSCT (76-79). It has also been reported as a late side effect in patients treated with autologous HSCT (80, 81). Salivary gland hypofunction has been associated with up to 67% of patients treated with thalidomide for metastatic carcinoid or islet cell tumors (82) and 43% of patients taking it for multiple myeloma (83); bendamustine for advanced bile duct cancer (84); 5-Fluorouracil and Leucovorin calcium for colon cancer (85). Aromatase inhibitors (anastazole, letrozole ) used as adjunctive treatment of
breast cancer have been associated with an increased frequency of sicca syndrome and joint pain (86). Temporary salivary gland hypofunction has been reported in patients taking adjuvant chemotherapy (combination of cyclophosphamide, epirubicin or methotrexate and 5-Fluorouracil for breast cancer (87). In this study, unstimulated, whole salivary flow rate decreased significantly during chemotherapy and remained lower than baseline at 6 months post-treatment. However, it increased again to baseline level one year after treatment. Stimulated whole saliva flow also decreased during treatment, but returned to baseline by 6 months after treatment. These patients also suffered from dry mouth (xerostomia) symptoms (87). Modest reduction in salivary gland secretions rates have also been reported in children during treatment for leukemia with a variety of cytotoxic chemotherapeutic regimens (88-90).

In summary, xerostomia can be treated using saliva substitutes, sugarless candies or gum, and bland mouth rinses. Some patients may benefit from the administration of pilocarpine (10 mg t.i.d.) or cevimeline (30 mg t.i.d.) to increase salivary output. Patients with significant xerostomia should also be closely monitored for the development of dental caries, which can be prevented by the daily use of 1.1% sodium fluoride dentifrice or gel. Oral hygiene and basic oral care are important to reduce the bacterial load in the oral cavity and risk for local infection, inflammation, and overall comfort. In general, alcohol-free mouth rinses, and bland oral care products, such as children’s toothpaste, are better tolerated in patients with oral mucosal inflammation and dry mouth than conventional products.

6. Dysgeusia and other Taste Disorders
Taste impairment has tremendous impact on quality of life; along with mucositis and xerostomia, it leads to significant alterations in diet and nutritional status of the patient (91). Dysgeusia is the distortion of the sense of taste and is often associated with ageusia, which is the complete lack of taste, and hypogeusia, which is the decrease in taste sensitivity. Taste is a sensation related to specialized receptors, selectively stimulated by molecules and ions of solutions in contact with these receptors. Smell modifies the experience of taste, as does temperature and texture. Taste buds are the anatomical structures that contain the receptor cells that mediate the sense of taste. These specialized organs are found on the tongue, soft palate, pharynx, larynx, uvula, upper third of the esophagus, and the buccal and labial mucosa. On the tongue, the taste buds are found in the papillae: the foliate papillae along the sides of the tongue, the fungiform papillae on the anterior portion of the tongue (oral tongue), and the circumvallate papillae on the posterior dorsum of the tongue. Each taste bud contains 50-100 taste receptor cells. These cells normally turn over every 10-11 days. Innervation of
the taste buds is supplied by the chorda tympani branch of the facial nerve (cranial nerve VII), supplying the fungiform papillae, the greater petrosal nerve (cranial nerve VII) supplying the palate, and the glossopharyngeal nerve (cranial nerve IX) supplying the foliate and circumvallate papillae. Some innervation from the foliate papillae may be provided by the chorda tympani. Fibers of the vagus nerve innervate the taste buds of the tonsillar region, epiglottis, pharynx, and esophagus. There are five basic tastes: sweet, sour, bitter, salty, and umami. All five tastes can be perceived in all areas of the tongue and palate where taste buds are located (92).

Taste alterations have been reported with a variety of cancer chemotherapeutic drugs, and can range from ageusia, hypogeusia, persistent bad taste (dysgeusia) or taste aversions (93). Drugs associated with taste disorders include bevacizumab and sunitinib for metastatic renal cell carcinoma (94). In a recent study, taste disturbances were reported in 84% of patients receiving adjuvant chemotherapy for breast cancer during chemotherapy, 22% 6 months after chemotherapy and 20% 1 year after chemotherapy. During chemotherapy, the most common complaint was of metallic taste or drug taste and hypogeusia. After chemotherapy, no one complained of drug taste or metallic taste but 11% experienced other types of dysgeusia and some experienced hypogeusia. In this study, the taste disorders were not correlated with whole salivary flow rates or complaints of xerostomia (87, 95). The chemotherapy consisted of cyclophosphamide, epirubicin or methotrexate and 5-Flourouracil. When chemotherapy was completed, patients received tamoxifen if their breast tumors were estrogen- or progesterone-receptor positive (87, 95). It is important to note that chemosensory dysfunction plays a very important role in declining nutritional status and quality of life. Patients with severe chemosensory disorders have significantly lower caloric intake, higher weight loss, and lower quality of life scores than patients with mild or moderate chemosensory complaints. These patients often experience these complications well past the time of active treatment with chemotherapy for advanced cancer (91).

7. Oral Graft-versus-Host Disease (GVHD)

Hematopoietic stem cell transplantation (HSCT), derived either from bone marrow or peripheral stem cells, is the treatment of choice for several leukemias, lymphomas, bone marrow failure syndromes and immunodeficiency disorders. It is also sometimes performed as salvage therapy for solid tumors. HSCT is characterized by the re-infusion of marrow or peripheral stem cells to constitute hematopoiesis following conditioning with high dose chemotherapy and/or radiation. The transplant can be defined as autologous (patient is donor) or allogeneic (someone else is donor). Autologous transplantation has a much lower risk of transplant-related mortality (2-10%) and residual immunosuppression than do allogeneic (20-50%) or unrelated donor (40-60%) transplants.
Acute and chronic graft versus host diseases (GVHD) are common complications of HSCT. Acute GVHD occurs within the first 100 days after allogeneic transplant in 18-70% of patients who receive GVHD prophylaxis (immunosuppressant medications). Factors that predispose to development of acute GVHD include HLA disparity, sex mismatching, multiple donor pregnancies, and age. Acute GVHD is seen at the time of or after evidence of engraftment, although hyperacute GVHD may occur earlier in severely mismatched or underprophylaxed patients. Primary target organs of acute GVHD are the skin, liver and gastrointestinal tract. These organs are clinically staged 0 to 4 based on the degree of involvement of each system, and then the patient is given an overall grade. Grade IV acute GVHD is almost 100% fatal (25).

Chronic GVHD occurs in approximately 60-80% of long term survivors of allogeneic HSCT and is a major cause of morbidity and mortality (96). Chronic GVHD is defined as occurring after 100 days post-transplant. Primary target organs of chronic GVHD are skin, oral cavity gastrointestinal tract, liver, conjunctiva, and other mucosal surfaces. The hematopoietic system may also be affected and present as thrombocytopenia. The risk of acquiring chronic GVHD is increased with increasing HLA incompatibility between recipient and donor. Therefore, recipients of unrelated donor marrow have a higher incidence of chronic GVHD. Other risk factors include a diagnosis of previous acute GVHD, the use of corticosteroids at day 100 post transplant, the use of non-T cell depleted bone marrow, older age of recipient or donor, and male recipients of female alloimmune donors.

Oral manifestations of chronic GVHD include xerostomia, and oral mucosal disease. The oral mucosa is most frequently involved by chronic GVHD. The oral cavity may be the primary or even the only site of chronic involvement. A lichenoid mucositis, which is the most common type of mucosal alteration in GVHD, may present as lacy white plaques, erythema, or ulceration. These lesions look like lichen planus. Pain is often a presenting symptom. Any oral site may be affected and there may be atrophy of the tongue. Severe gingival recession and early loss of teeth has been reported in oral GVHD (97). The differential diagnosis for oral ulcers in the setting of HSCT includes recrudescent Herpes Simplex infection or cytomegalovirus stomatitis (52, 98). Cultures for viral organisms and biopsy are advised to determine the diagnosis for oral ulcers in this setting since oral viral infections can occur concomitantly with GVHD. Xerostomia affects approximately 50% of patients (99, 100). Many have measurable decreased salivary flow rates, and a history of total body irradiation increases this risk (101-103).

Patients with GVHD are susceptible to infections such as herpetic stomatitis, cytomegalovirus infections, Epstein-Barr infections in the form of oral hairy leukoplakia and deep fungal infections. Recrudescent HSV often occurs at sites of injury such as on the lips after sun exposure or intraorally after dental treatment. Fibrosis and limitation of opening of the mouth has been seen in 73% and 26
% of patients with and without chronic GVHD and is most often seen in patients with the scleroderma-like skin changes of GVHD.

**Management of Chronic Oral GVHD:**
Persistent painful oral erosions, lichenoid changes, and ulcerations may persist as the only sign of chronic GVHD in some patients. The goals of therapy are treatment of specific oral lesions, pain control, alleviation of xerostomia, prevention of dental caries and maintenance of oral health.
The painful erosive and ulcerative lesions generally are treated with topical corticosteroid preparations such as fluocinonide and clobetasol gels, or dexamethasone and betamethasone elixirs. Application of topical corticosteroids in the oral cavity is hampered by the lack of a specialized delivery system. This can be overcome partially by more frequent application (3-6 times per day), delivery of the drug in a custom tray (for gingival lesions) and compounding medication into an occlusive base (Orabase™ dental paste; Colgate Pharmaceuticals). Patients should also be advised to refrain from eating or drinking for 30 minutes after application, in order to increase contact time with the affected tissues. In general, gels are used for localized ulcerative lesions, and elixirs are used for more widespread lesions. Intralesional corticosteroid injections can be useful when the oral mucosa is affected by one or two large ulcers. Typical dosing of triamcinolone acetonide provided as 10 mg/ml or 40 mg/ml is 5 mg/cm² injected into the base of the ulcer (25). Mixing this solution with local anesthetic can help make the injection more comfortable for the patient. The same can be accomplished by anesthetizing prior to injection. Topical cyclosporin has been shown to provide some benefit (104).
Opportunistic infections such as oral candidiasis, deep fungal infections, herpetic infections and Gram negative bacterial infections may occur as a result of the systemic immunosuppression, the use of topical steroids, antibiotics and the presence of xerostomia. Therefore close follow-up is indicated. Diagnostic tests should be used as necessary to diagnose lesions with atypical presentations.
Local pain control may be provided by soothing mouth rinses such as saline and anesthetic rinses such as 2% viscous lidocaine or diclonine hydrochloride. These anesthetics should be held in the mouth for 2 minutes, and expectorated, being careful to avoid swallowing as this can cause pharyngeal anesthesia and increases risk for aspiration. Pain medications should be considered, starting with non-narcotics, progressing to opiates that contain codeine or hydrocodone to stronger opiates such as meperidine and morphine as needed. If pain is long term, which is often the case, consideration must be given to the issue of dependency as well as gastrointestinal and neurological side effects.
Xerostomia can be treated as described in Section 5, Salivary Gland Hypofunction and Xerostomia.

8. Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ)

Intravenous bisphosphonates were first introduced for the treatment of bone metastases in 1991. Since then, bisphosphonates have become the standard of care for metastatic disease spread to bone from breast, lung and prostate cancer; treatment of multiple myeloma; and management of hypercalcemia of malignancy. Intravenous bisphosphonates are also effective in preventing osteopenia in patients with prostate cancer undergoing androgen deprivation therapy. Bisphosphonates are potent inhibitors of osteoclast activity and induce apoptosis. They have also been shown to inhibit vascular endothelial growth factor (VEGF), angiogenesis and endothelial proliferation (105). Bisphosphonates have been shown to prevent skeletal-related events, reduce bone pain and improve quality of life. Oral bisphosphonates are used in the prevention and treatment of osteoporosis in women and men. Although far less common, there have been cases reported of osteonecrosis of the jaw occurring in patients taking the less potent oral bisphosphonates.

Starting in 2003, a growing number of case reports and case series have been published that link bisphosphonate administration with osteonecrosis of the jaw and facial bones, a condition that had been extremely rare. The mechanism that underlies the association between the drug and this complication is not understood. Proposed explanations include infection, loss of blood supply, or suppression of bone turnover. Bisphosphonate-associated osteonecrosis of the jaw is defined as the unexpected development of necrotic bone in the oral cavity of a patient receiving bisphosphonate therapy who has not received radiation therapy to the head and neck.

The American Academy of Oral and Maxillofacial Surgeons (AAOMS)’s position paper on this topic (106, 107) further defines BRONJ, based on three necessary conditions that need to be true simultaneously:

1. Current or previous treatment with a bisphosphonate
2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks
3. No history of radiation therapy to the jaws

Conditions commonly misdiagnosed as BRONJ include alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporo-mandibular joint dysfunction (TMD) (106, 107).

BRONJ can occur spontaneously, with dental infection, or after dental treatment. It is usually painful, but reports indicate that up to 1/3 of cases may be asymptomatic. The typical clinical presentation is an area of exposed non-vital bone. The gingival or mucosal tissues surrounding the necrotic bone are usually inflamed and sensitive to palpation which makes it difficult for the patient
to perform oral hygiene procedures. Attempts to debride the necrotic bone often lead to enlargement of the defects and no healing. The sharp edges of the necrotic bone often traumatize the adjacent soft tissue, including the lateral tongue, which lead to ulceration and pain. If teeth adjacent to the defects are periodontally involved, this can lead to further bony necrosis and loss of teeth. Necrotic bone often sequesters and spontaneously sheds over time. Some cases have progressed to include loss of sensory innervation and pathological fracture (108).

A large population-based study attempted to estimate the risk of ONJ and intravenous bisphosphonate use, based on tumor registry data from the Surveillance, Epidemiology and End Results (SEER) program linked to Medicare claims data (109). A total of 16,073 cancer patients diagnosed between January 1986 and December 31, 2002, and treated with intravenous pamidronate and/or zoledronic acid between January 1, 1995 and December 31, 2003, were matched at a 2:1 ratio with 28,698 bisphosphonate non-users and 14,349 bisphosphonate users. The groups were matched on several clinical factors, including cancer type, age, sex, and risk factors for BRONJ (diabetes, alcoholism, smoking, obesity, hyperlipidemia, pancreatitis, and chemotherapy) (109). The use of intravenous bisphosphonate was associated with an increased risk of jaw or facial bone surgery (Hazard Ratio [HR] =3.15; 95% C.I. = 1.86 - 5.32), and an increased risk of being diagnosed with inflammatory conditions or osteomyelitis of the jaw (HR=11.48, 95% C.I. = 6.49 - 20.33) compared with non-use. The absolute risk at 6 years for any jaw toxicity was 5.48 events per 100 patients using intravenous bisphosphonates versus 0.30 events per 100 patients not using such drugs. The risk of each outcome increased as cumulative dose increased. One of the limitations of this study was that there is no ICD-9 code for BRONJ. Therefore, it is not absolutely certain that these events represented BRONJ. However, it is the first large, population-based estimate of the risk of ONJ for intravenous bisphosphonate use published (109). Another study attempted to estimate the incidence of BRONJ, based on retrospective review of patient medical records from Massachusetts General Hospital (110). In this study of 477 patients, the incidence of BRONJ associated with intravenous bisphosphonates was at least 3.8 per 100 patients with multiple myeloma, 2.5 per 100 patients with breast cancer, and 2.9 patients per 100 with prostate cancer during the 5 year period studied (110).

It is important to bear in mind that a history of underlying dental problems, such as dental extraction or periodontal disease, is a major risk factor for BRONJ (111). For example, in Marx’s case series of 119 patients with BRONJ, the most common dental comorbidity was clinically and radiographically apparent periodontitis, which was present in 84% of patients. Event inciting the BRONJ was tooth extraction in 38%, existing periodontal disease in 29%, and periodontal surgery in 11%. Furthermore, the AAOMS also identified anatomic factors, such as the presence of prominent bone
with thin overlying mucosa, as seen with lingual tori and the mylohoid ridge on the mandible, and palatal tori on the maxilla (106, 107).

**Prevention and Treatment of BRONJ:**
Currently, there is no effective treatment for BRONJ. There is a tremendous gap in our understanding of the pathophysiology of this disease, which impedes the development of new and efficacious therapies. Nonetheless, guidelines for management have been published, all with a common theme of minimally invasive therapy. Conservative therapy includes good oral hygiene, the use of antimicrobial rinses, such as 0.12% chlorhexidine, and avoiding trauma to bone, gentle debridement of loose necrotic bone, and treating active infection. Time heals some lesions treated conservatively. Most guidelines advocate treatment of active infection and eliminating dental risk factors prior to initiation of therapy, establishing routine dental care and oral hygiene, maintenance of regular dental recall, and education of the patient (112, 113). Since there currently is no effective treatment, prevention is critical.

AAOMS and Ruggiero et al. (106, 107, 113) have proposed the following clinical staging for BRONJ:

- **Stage 1**  Exposed, necrotic bone that is asymptomatic
- **Stage 2**  Exposed, necrotic bone associated with pain and infection
- **Stage 3**  Exposed, necrotic bone in patients with pain, infection, and pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border.

Patients with stage 3 BRONJ may require surgical therapy to debride necrotic bone since at this stage, the volume of involvement is usually greater (106, 107, 113).

The AAOMS Guidelines for Management and Prevention of BRONJ are summarized in the following. These guidelines are intended for the use by dentists and physicians treating patients at risk for BRONJ:

**For Patients with Bisphosphonate-Induced Osteonecrosis of the Jaw:**
1. Maintain oral hygiene as meticulously as possible.
3. Treat infection aggressively with systemic antibiotics and antiseptic mouthwashes.
4. Avoid compression of nervous tissue and rubbing of soft tissue across bone.
5. Consider switching from an intravenous aminobisphosphonate therapy to clodronate, taking into account potential to reduce ONJ (which has not yet been proven) versus the benefits of therapy.

For Patients About to Start Bisphosphonate Therapy:

1. Evaluate the oral cavity with clinical and radiographic examination, at least a panoramic radiograph.
2. Develop an individual risk profile for the patient:
   a. History of prior head and neck radiation
   b. Presence of oral disease/infections such as partially erupted third molars, teeth with significant bone loss, dentures (assess fit)
   c. Eliminate all oral risk factors if possible. Avoid elective jaw procedures that require bone healing.
   d. Establish routine oral hygiene practices with the patient and educate regarding the signs, symptoms, and sequelae of BRONJ.
   e. Establish a brief oral examination at each follow-up oncology visit – refer to dentist with any suspicious findings.
   f. Carefully consider choice of bisphosphonate.

It is suggested that if necessary dento-alveolar surgery is performed prior to initiation of bisphosphonate therapy, one should allow 4-6 weeks for the bone to heal before starting therapy.

For Patients Receiving Bisphosphonates with No Signs of BRONJ:

1. If less than 3 months of therapy, follow above.
2. If greater than 3 months, follow above AND
   a. Dental recall every 6 months
   b. Check and adjust removable dentures to remove potential for soft tissue trauma
   c. Conservative dental treatment, avoiding surgical procedures, e.g. Root canal therapy instead if extraction if possible.
   d. Follow up dental procedures to ensure complete healing.

A team approach with the oncologist and dental professional working closely together to ensure the optimal health of the patient is advocated.

In regards to the question of the advisability of discontinuing intravenous bisphosphonates prior to dental treatment, it should be remembered that oncology patients benefit greatly from the therapeutic effects of these drugs by controlling bone pain and the incidence of pathologic fractures.
Discontinuation of intravenous bisphosphonates offers no short-term benefit. However, if systemic conditions permit, long term discontinuation of therapy might be beneficial in stabilizing established sites of BRONJ and preventing further sites of involvement and associated pain and impact on quality of life. However, the risk and benefits must be discussed by the oncologist and dental professional with the patient’s overall quality of life kept in mind (107).

III. 2010 PUBLICATIONS: SPECIAL SYSTEMATIC REVIEWS
A. Nine Systematic Reviews on Oral Complications of Cancer Therapies Published in August 2010 in the Journal Supportive Care in Cancer
A special publication related to the current topic appeared in a special section counting 130 pages in the August 2010 issue of the journal Supportive Care in Cancer, which is the official journal of the Multinational Association of Supportive Care in Cancer (MASCC). With participation of numerous internationally recognized experts in the field, The Oral Care Study Group of the MASCC in collaboration with the International Society of Oral Oncology (ISOO) completed nine systematic reviews of the scientific literature regarding cancer patients in the following areas: 1) oral fungal infections (114), 2) viral infections (115), 3) dental disease (116), 4) orofacial pain (117), 5) trismus (118), 6) dysgeusia (119), 7) bisphosphonate osteonecrosis (BON) (120), and 2 systematic reviews on salivary gland hypofunction and xerostomia: 8) prevalence, severity and impact on quality of life (121), and 9) management strategies and economic impact (122). Additionally, a report on osteoradionecrosis in cancer patients (123) was published in that special section, along with an introductory message (124) and a description of the methodology applied in during the systematic reviews (125). It should be noted that the first author of this literature review report, Dr. Carol Anne Murdoch-Kinch, has co-authored the two reviews [6) and 7]) on salivary gland hypofunction and xerostomia (121, 122).

The reason for undertaking such a massive literature review is that oral complications are commonly experienced by patients undergoing cancer therapies. The review aims to determine the prevalence, relationship with quality of life, economic impact, and formulation of guidelines based on the quality of the literature for each oral complication. Abstracts and citations for these reviews may be viewed and downloaded free of charge at: http://www.springerlink.com/content/0941-4355/18/8/

Electronic copies of each article may be downloaded for a fee of $34 each.

The review by Hong et al. on dental disease in patients undergoing cancer therapy was supported by a federal grant and is available for free, which is indicated by the bright orange-red button “Open Access” at the website. The report may be downloaded by clicking on the “Download PDF” or
The conclusion of systematic review of 64 research reports published between 1990 and 2008 was that the overall prevalence of dental caries was almost 30% (28.1%), and dental infections/abscess during chemotherapy was 5.8%. The use of fluoride products and chlorhexidine rinses are beneficial in patients who are post-radiotherapy. However, the authors lament the lack of clinical studies on the extent and severity of dental disease that are associated with infectious complication during cancer therapy.

B. Cochrane Systematic Reviews

Cochrane Reviews are systematic reviews of primary research in human health care and health policy. They investigate the effects of interventions for prevention, treatment and rehabilitation. Cochrane Reviews are internationally recognized as the highest standard in evidence-based health care. A Cochrane Review is a scientific investigation in itself, with a pre-planned Methods section and an assembly of original studies (predominantly randomized controlled trials (RCTs), but also sometimes, non-randomized observational studies) as their ‘subjects’. The results of these multiple primary investigations are synthesized by using strategies that limit bias and random error. These strategies include a comprehensive search of all potentially relevant studies and the use of explicit, predefined, reproducible criteria in the selection of studies for review. Primary research designs and study characteristics are appraised, data are synthesized, and results are interpreted. Each systematic review addresses a clearly formulated question and is updated regularly. More information is available at: [http://www.cochrane.org/cochrane-reviews](http://www.cochrane.org/cochrane-reviews)

Four systematic reviews were conducted by the Cochrane Collaboration on topics this report concerns, namely on oral mucositis and candidiasis in patients receiving cancer treatment:

**Oral Mucositis**

Two systematic reviews last updated in 2007 pertained specifically to mucositis in patients with cancer receiving treatment: One on preventing oral mucositis (126) and one on interventions for treating oral mucositis (36) in this patient group.

The reviewers conclude that of the 33 interventions included in trials, 12 showed some evidence of benefit (although sometimes weak) for either preventing or reducing the severity, but only the following substances were shown to have some positive effect in more than one study included: ice chips, hydrolytic enzymes, and Chinese medicine. Thus, more clinical trials are warranted. Summaries of these two reviews that include a brief paragraph in plain language can be accessed at:
Oral Candidiasis

Two similar systematic reviews regard oral candidiasis in patients with cancer receiving treatment: One review was on preventing oral candidiasis (44), which was conducted in 2007 with unchanged conclusions confirmed in 2009. The other review conducted in 2010 examined interventions for treating oral Candidiasis (50).

Summaries of these two reviews that include a brief paragraph in plain language can be accessed at: http://www.thecochranelibrary.com/details/browseReviews/577915/Oral-candidiasis.html

IV. CONCLUSIONS

The cancer patient faces a number of significant potential oral complications of his/her therapy, whether receiving myelosuppressive chemotherapy or HSCT. Dental treatment decisions require an understanding of the staging of the patient’s cancer and prognosis for survival, the types of therapy planned, timing of therapy, patient’s motivation and ability to cooperate, and anticipated oral complications of treatment. In general, the dental care provider can help prepare the patient prior to therapy by treating any active or potential dental infection and by providing the patient education and supportive care during treatment. The dental treatment and oral management of patients with cancer should include an oral evaluation, including periodontal examination, before the patient begins cancer treatment. This evaluation will help to prevent or mitigate oral complications associated with chemotherapy as well as systemic sequelae of oral infection. Patients about to receive intravenous bisphosphonates should also have an oral assessment and treatment in order to prevent BRONJ. Many of the oral complications of cancer therapy, such as mucositis, oral candidiasis, and oral viral infections, are managed by the oncology team, whereas GVHD-associated xerostomia and dental disease is the responsibility of the dental team. Therefore, the general dentist or dental specialist who is asked to provide dental care for the oncology patient should be aware of current recommendations for care and be familiar with their scientific basis and be prepared to consult with the oncology team in order to provide the most appropriate care for the patient during cancer treatment -- and for the rest of his/her life.
V. BIBLIOGRAPHY


### VI. LIST OF ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Text Expression</th>
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<tbody>
<tr>
<td>AAOMS</td>
<td>American Academy of Oral and Maxillofacial Surgeons</td>
</tr>
<tr>
<td>ALL</td>
<td>acute lymphocytic leukemia</td>
</tr>
<tr>
<td>AML</td>
<td>acute myelogenous leukemia</td>
</tr>
<tr>
<td>APC</td>
<td>adenomatosis polyposis coli</td>
</tr>
<tr>
<td>BRONJ</td>
<td>bisphosphonate-related osteonecrosis of the jaw</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
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<tr>
<td>CLL</td>
<td>chronic lymphoid leukemia = B-cell chronic lymphocytic leukemia (B-CLL)</td>
</tr>
<tr>
<td>CML</td>
<td>chronic myelogenous leukemia</td>
</tr>
<tr>
<td>CS</td>
<td>Cowden syndrome = multiple hamartoma syndrome</td>
</tr>
<tr>
<td>GS</td>
<td>Gardner’s syndrome</td>
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<tr>
<td>GVHD</td>
<td>graft versus host disease</td>
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<tr>
<td>HLA</td>
<td>human leukocyte antigen system</td>
</tr>
<tr>
<td>HSCT</td>
<td>hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>HVZ</td>
<td>recurrent Herpes zoster = shingles</td>
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<tr>
<td>ISOO</td>
<td>International Society for Oral Oncology</td>
</tr>
<tr>
<td>KOT</td>
<td>keratinizing odontogenic tumors</td>
</tr>
<tr>
<td>MASCC</td>
<td>Multinational Association of Supportive Care in Cancer</td>
</tr>
<tr>
<td>MEN III</td>
<td>multiple endocrine neoplasia syndrome</td>
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<td>MM</td>
<td>multiple myeloma</td>
</tr>
<tr>
<td>MTC</td>
<td>medullary thyroid carcinoma</td>
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<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
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<tr>
<td>NBCCS</td>
<td>nevoid basal cell carcinoma syndrome</td>
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<tr>
<td>ONJ</td>
<td>osteonecrosis of the jaw</td>
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<tr>
<td>OPC</td>
<td>oropharyngeal candidiasis</td>
</tr>
<tr>
<td>PNP</td>
<td>paraneoplastic pemphigus</td>
</tr>
<tr>
<td>PTEN</td>
<td>phosphatase and tensin homolog</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RET</td>
<td>Rearranged during Transfection</td>
</tr>
<tr>
<td>SJS</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>SS</td>
<td>Sweet’s syndrome = acute febrile neutrophilic dermatosis</td>
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<tr>
<td>TPN</td>
<td>total parenteral nutrition</td>
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</table>