Original Article

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MEDICATIONS INFLUENCING IMMUNE RESPONSE AND WOUND HEALING

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Abstract

This paper offers an overview of the 3 primary groups of medications that have the potential to directly or indirectly influence the immune response: antineoplastic agents, bisphosphonates, and steroids. Antineoplastic agents in high-dose chemotherapy regimens have been a foundation of oncology management of disseminated disease for several decades. New generations of cytotoxic agents with increased capability for increased tumor cell cytotoxicity have evolved over time. Current regimens are highly specific for tumor cells, yet some can produce clinically significant compromise in the patient's systemic and tissue-based immune response as well as in wound healing capability. The dentist can offer a pivotal contribution to the oncology team by preventing or ameliorating these and related side effects. In particular, the literature provides compelling evidence for eliminating high-risk oral lesions of the dentition, periodontium, periradicular region, and mucosa prior to initiating myelosuppressive chemotherapy. Novel molecular approaches to cancer therapy, including monoclonal antibodies, are changing the profile of oral and systemic toxicities. Though such agents are beginning to facilitate new successes in oncology practice, further research is needed.

Bisphosphonates, in both intravenous and oral forms, are increasingly used to improve mineral bone density in patients with osteoporosis, multiple myeloma, and other diseases and conditions. Osteoporosis is associated not only with postmenopausal women, but also with several medications used to treat breast cancer, gastric acidity, and other conditions. Bisphosphonates directly suppress osteoclast activity and angiogenesis, and, ultimately suppress wound healing and immune response.

Steroids, in both topical and systemic forms, are used to suppress undesirable immune responses and manage a wide variety of systemic and intraoral mucosal disorders, including recurrent aphthous ulcerations and lichen planus. Steroids can be a mainstay in pharmacologic immunomodulation when proper care is taken to minimize steroid-induced side effects.

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Introduction

The immune response is the primary host defense against microorganisms, including bacteria, viruses, and fungi. The innate and acquired immune responses are synergistic, and play a vital role in the overall host defense mechanism.

Selected systemic diseases and conditions require medication for optimal management. However, both the clinician and the patient must assess the risks and benefits before proceeding with pharmacologic therapy. For example, antineoplastic agents are likely to cause mild, moderate, and/or

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severe side effects associated with various pharmacologic classes, doses, regimens, and mechanisms of action of these agents. Cancer chemotherapy should be managed by a qualified physician who is experienced in using such antineoplastic agents, and in a clinical facility that is appropriate to care for both the cancer and the potential medical complications that may result from chemotherapy.

We address three primary groups of medications[i] that have the potential to either directly or indirectly influence the immune response:
- Antineoplastic agents
- Bisphosphonates
- Steroids

Concurrent immunosupportive therapies, such as antibiotics and antimicrobial rinses, are frequently used with these medications.

Antineoplastic agents primarily function to prevent or suppress the growth, development, or metastases of neoplastic cells. The ideal objective of cancer treatment is to reduce the cancer cell population to zero.[1] Many antineoplastic drugs are myelosuppressive, thus resulting in dramatic reduction of circulating leukocytes as measured by white blood cell count and/or total granulocyte count, and total platelet count. Contemporary oncology practice often uses combinations of antineoplastic agents in multiple cycles for patients collectively exhibiting a range of solid tumors. In addition, chemotherapy is increasingly administered concurrently with high-dose head and neck radiation for oral malignancies that have metastasized beyond the primary initial site of occurrence. This evolution of pharmacologic regimens for metastatic cancer continues to produce clinically significant side effects, including compromised oral, systemic, and tissue immunity, accompanied by compromised wound healing.

Bisphosphonates primarily function to enhance bone mineral density (generally measured with dual-energy x-ray absorptiometry (DEXA) and expressed as a "T score"), and reduce pathogenic fractures (e.g., as measured by hip fracture reduction). Pharmacologically, these agents reduce osteoclast function.[2] Bisphosphonates are associated with impaired angiogenesis[3] and impaired wound healing,[4] which impede delivery of immune cells to the site of microbial challenge, and therefore indirectly result in immunosuppression. Bisphosphonates are also associated with osteonecrosis of the jaw (BIONJ).[5,6]

Steroids primarily function to suppress undesirable immune reactions. Pharmacologically, this is achieved through a number of mechanisms, including: (1) gene expression that leads to reduction in the synthesis of important mediators of the inflammatory process (such as prostaglandins and leukotrienes);[7] (2) suppression of cyclooxygenase synthesis resulting in decreased neutrophil, monocyte, and eosinophil chemotaxis, as well as inhibition of vascular and inflammatory responses to prostaglandins;[8] (3) inhibition of white blood cell production;[8] (4) inhibition of adhesion molecule synthesis in endothelial cells, which impairs attachment of inflammatory cells and hinders their recruitment to sites of inflammation;[8] (5) inhibition of macrophage-driven antigen phagocytosis, which is necessary for development of some immune responses;[7] and, (6) suppression of antibody production.[9] Topical or systemic steroid therapy is used for a wide variety of systemic and oral mucosal disorders. However, because of the profound and varied metabolic effects caused by steroids, they can exacerbate many systemic conditions including, but not limited to, hypertension, diabetes mellitus, gastrointestinal ulcers, cataracts, mental illness, tuberculosis, and fungal infections.[10] The immune suppression that results from steroid use may also lead to infections by opportunistic or indigenous microorganisms.

Antineoplastic agents

High-dose chemotherapy can directly and indirectly result in oral toxicities, including impairment of both wound healing and immune response (Table 1).[11,12] The combination of these direct and indirect effects can compromise cancer patients' quality of life.[13,14] In some cases, the oral lesions can result in the need to limit the dose of subsequent chemotherapy to allow the lesion to heal; in the

Table 1. Oral complications of cancer chemotherapy

Direct Toxicities	Indirect Toxicities
Oral mucositis	Myelosuppression • Neutropenia • Immunosuppression • Anemia • Thrombocytopenia
Neurotoxicity • Taste dysfunction • Dentinal hypersensitivity	
Temporomandibular dysfunction	Infection • Viral • HSV, VZV, CMV, EBV, other • Fungal • *Candida*, *Aspergillus*, other • Bacterial
Dental and skeletal growth/ development (pediatric patients)	

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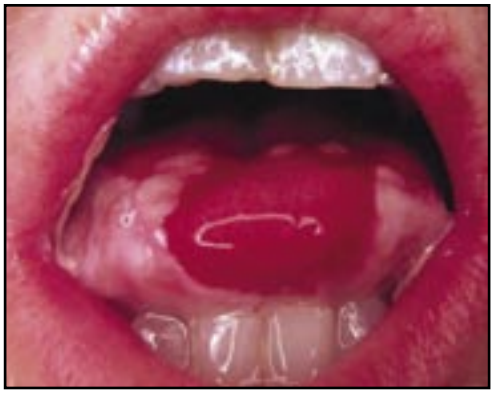
[i] The group of medications used to permit "acceptance" of a transplanted organ is discussed in another article in this issue of *Grand Rounds*; please see "Dental Implications for the Immunocompromised Organ Transplant Patient."

Figure 1: Severe oral mucositis in a patient on antineoplastic therapy



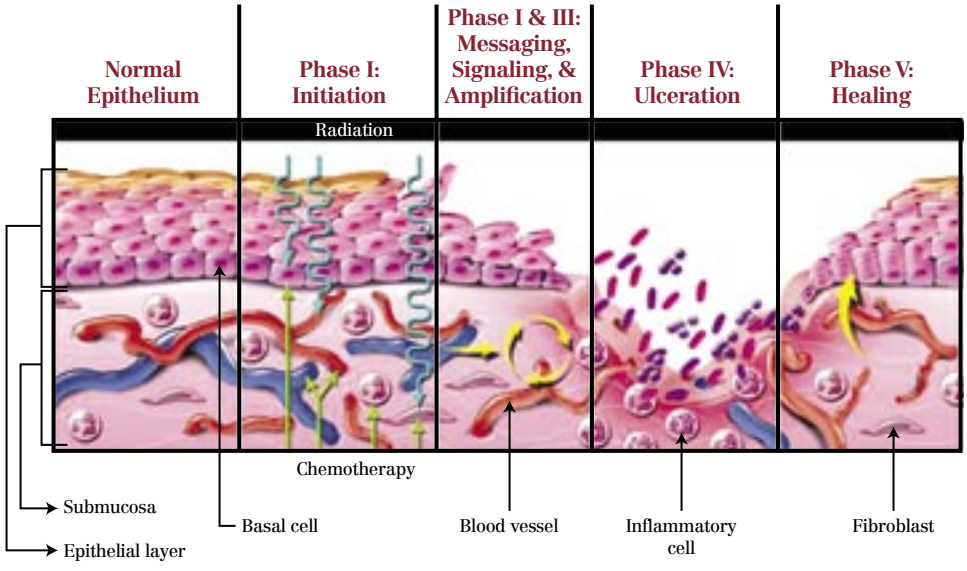
The lesion is characterized by extensive, painful ulcerations of non-keratinized mucosa. *(Photo courtesy of Douglas E. Peterson, DMD, PhD)*

neutropenic patient, this can contribute to mortality.[12] Severe oral mucositis is characterized by extensive, painful ulcerations of non-keratinized mucosa (Figure 1). Chemotherapy-induced alimentary tract mucosal injury in cancer patients has been the subject of increasingly sophisticated research over the past decade.[11,12,16,17] This progress has included development of a pathobiologic model (Figure 2).[18]

Frequencies of oral mucositis vary in chemotherapy patients; estimates include 10% associated with adjuvant chemotherapy, 40% associated with primary chemotherapy, and 80% associated with hematopoietic stem cell transplant.[13,14] Incidence and severity of oral and gastrointestinal mucositis can be influenced by multiple variables, including drug class and mechanism of action of each chemotherapeutic agent (Figure 3), as well as dose intensity and frequency of administration.[13,14,19] While use of chemotherapy regimens is based on a number of cancer disease parameters including histologic type of the neoplasm, it is the chemotherapy, not the cancer itself, that directly governs risk for oral and gastrointestinal mucosal toxicity. Examples of this wide variation in mucositis incidence and severity have recently been reported across various cancer patient cohorts:[19]

- Conventional chemotherapeutic regimens for non-Hodgkin's lymphoma are associated with 3-10% incidence of severe oral mucositis. However, most (>90%) comparable patients do not develop severe oral mucosal injury.
- Multi-cycle platinum-based regimens, with or without concurrent radiotherapy, are associated with a low incidence of severe oral mucositis in lung cancer patients. However, radiotherapy in these patients is associated with >15% incidence of

Figure 2: Pathology model of progression of ulceration (mucositis) and wound healing of patients on antineoplastic therapy



The paradigm illustrates the continuum of mucosal injury and eventual repair that involves both oral epithelium and the underlying oral mucosal connective tissue. Phase I ("Initiation") begins within hours of first administration of high-dose cancer therapy. Phases II and III then emerge during the first few days following this initial cancer therapy, and are characterized by a genetically-governed upregulation in proinflammatory cytokines, which can then further amplify mucosal injury via positive feedback loops. It is important to note that the inflammatory pathways in Phases I-III are primarily or exclusively subclinical; clinical signs and symptoms of oral mucositis are typically absent.

Phase IV is characterized by the hallmark clinical stage of oral mucositis, with overt, painful, and frequently extensive oral ulcerations. These lesions will usually resolve during the 2-4 weeks after high-dose chemotherapy is discontinued, as illustrated in Phase V.

This current paradigm is in marked contrast with the concept held until the late 1990s that oral mucositis represents results of injury to only oral epithelial basal cells. The contemporary pathobiology modeling has created new opportunities for development of targeted drug therapies designed to reduce severity of clinically significant oral mucosal toxicity.

Figure 3. Incidence of oral mucositis in relation to type of cancer therapy

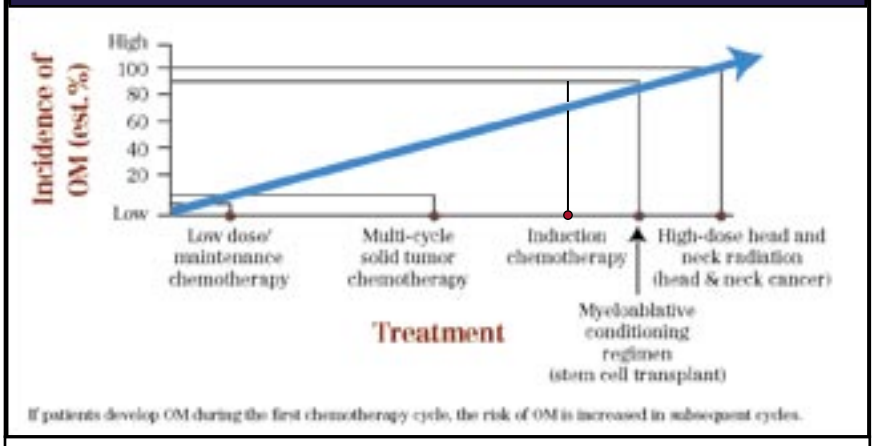


Figure courtesy of Douglas E. Peterson, DMD, PhD

severe esophageal (versus oral) mucositis.

- Conventional chemotherapy in advanced colorectal cancer patients is not likely to be associated with producing severe oral mucositis. In contrast, however, the overall incidence of diarrhea in these patients is high (16%), increasing to approximately 25% when both irinotecan and oxaliplatin are incorporated into the cancer treatment regimens.

Current research includes pursuit of possible mechanistic-based factors that are principally responsible for this variable

Table 2. Management suggestions relative to invasive dental procedures in patients undergoing antineoplastic therapy

Medical Status	Guideline	Comments
Patients with chronic indwelling venous access catheters (e.g., Hickman device)	Regimens recommended by the American Heart Association[20] for infective endocarditis prophylaxis are often used.	There is no definitive scientific evidence detailing infectious risk for these lines following dental procedures. This recommendation is empiric.
Neutrophils		Order CBC with differential
>1,500 cells/mm^3	Prophylactic antibiotics for neutropenia are usually not necessary.	Other indications for prophylaxis may be present.
<1,500 cells/mm^3	Antibiotic prophylaxis should be considered. Regimens recommended by the American Heart Association[20] for infective endocarditis prophylaxis are often used. However, clinical judgment is critical: if infection is present or neutropenia is severe, more aggressive antibiotic therapy may be indicated, based on consultation with an infectious disease specialist.	If organisms are known or suspected, appropriate adjustments to antibiotic regimens should be made based on sensitivities.
Platelets[a]		Order platelet count and, if indicated, coagulation tests
>75,000 cells/mm^3		
40,000 - 75,000 cells/mm^3	No additional platelet support needed. Platelet transfusions are optional; consider administering preoperatively and 24 hours later. Additional transfusions are based on clinical course.	Use techniques to promote establishing and maintaining control of bleeding (e.g., sutures, pressure packs, minimization of trauma).
<40,000 cells/mm^3	Platelets should be transfused 30 minutes before surgical procedure; obtain STAT platelet count, transfuse regularly to maintain counts above 30,000 - 40,000 cells/mm^3 until initial healing has occured.	In addition to above, consider using hemostatic agents (e.g., microfibrillar collagen, topical thrombin, fibrin glues). Monitor sites carefully.

[a] Assumes that all other coagulation parameters are within normal limits and that platelet counts will be maintained at or above the specified level until stabilization/healing has occurred.

Adapted with permission from Schubert MM, Epstein JB, Peterson DE. *Oral complications of cancer therapy.* In: Yagiela JA, Dowd FJ, Neidle EA (eds). Pharmacology and Therapeutics for Dentistry, 5th Edition, page 803.[21] Copyright Elsevier (Mosby-Year Book Inc.) 2004.

Table 3. Guidelines for dental extractions in patients scheduled to undergo myelosuppressive chemotherapy

Timeframe, Parameter	Guidelines
Scheduling extraction if neutrophil count expected to decrease <500 cells/mm^3	Perform extraction at least 10 days prior to neutrophil count becoming <500 cells/mm^3
Day of extraction, if absolute neutrophil count <1,500 cells/mm^3	Consider use of a broad-spectrum prophylactic antibiotic regimen
30 minutes prior to extraction, if platelet count <40,000 cell/mm^3	Administer random donor or histocompatibility-matched platelets (as available)
During extraction	Minimize surgical trauma, with alveolectomies as necessary to achieve primary closure with multiple interrupted sutures
After extraction	Minimize use of hemostatic packing agents within extraction sites

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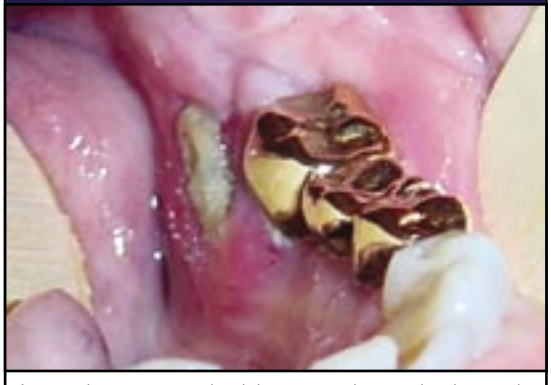
expression of oral and gastrointestinal mucositis across cancer patients.

In some cases, oral mucositis necessitates chemotherapy dose reduction or schedule modifications in order to reduce severity of future oral mucosal injury. For example, among patients undergoing chemotherapy for solid tumors or lymphomas, dose reduction was twice as common after treatment cycles for patients with mucositis than for those without mucositis.[16] This compromise in optimal dosing schedule can affect tumor response and thus patient survival. In addition, oral mucositis can contribute to increased healthcare costs associated with (a) extended hospital stays, (b) need for total parenteral nutrition, (c) infection management, and (d) nutritional support.[13]

Dental management of patients taking antineoplastic agents. It is important that the oncologist and dentist maintain clear communication in order to provide maximum preventive and therapeutic management. Elements of the health professional consultation include both the patient's medical status and an integrated oncology/dental management plan (relative to oral disease before, during, and after cancer treatment).[14] Management suggestions relative to invasive dental procedures in patients currently receiving antineoplastic therapy are outlined in Table 2.

Figure 4. Lower left lingual area of peridontium in a patient on antineoplastic therapy



Increasing compromised bone matrix can lead to pain and clinically evident bone exposure.

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A limited number of studies address guidelines for dental extractions, endodontic management, and related interventions in patients scheduled to receive high-dose chemotherapy. However, procedures associated with dental extractions have been used by clinicians for many years, based on historical retrospective studies.[22,23] Guidelines for dental extractions in patients scheduled to undergo myelosuppressive chemotherapy are outlined in Table 3.

New trends in oncology practice based on "targeted" therapies. Targeted cancer therapies, including monoclonal antibodies, are being utilized with increasing frequency in clinical oncology practice.[24] For example, potential targets of monoclonal antibodies are growth factor receptors, signaling kinases, and transcription factors.[24] These novel molecular approaches are in turn causing a change in expression of toxicities among various cancer cohorts, including diarrhea and oral mucosal ulceration.[24] The potential impact on immune response and wound healing relative to oral toxicities requires additional study.

Bisphosphonates

Management of cancer patients may also include bisphosphonates to control metastatic bone lesions through impairment of osteoclast function.[6] A severe complicating factor is BIONJ with associated osteomyelitis, although most BIONJ patients exhibit osteonecrosis without osteomyelitis.[5,6] Maxillary, mandibular, and soft-tissue lesions, secondary to long-term bisphosphonate use in patients with cancer, have been increasingly reported in the literature.[25-28] Over time, the accumulation of compromised bone matrix can lead to pain and clinically evident bone exposure that can be difficult to manage clinically (Figure 4).[28] Since there are currently no evidence-based guidelines for treatment of BIONJ, prevention may be the best approach to managing this complication.[26]

Steroids

Topical or systemic steroid therapy is indicated for a wide variety of systemic and oral mucosal disorders. Common uses for systemic steroids include endocrine disorders (primary or secondary adrenal insufficiency), rheumatic

disorders (rheumatoid arthritis), collagen diseases (systemic lupus erythematosus), dermatologic diseases (pemphigus, pemphigoid, lichen planus, erythema multiforme), respiratory diseases (sarcoidosis, chronic obstructive pulmonary disease), hematologic diseases (idiopathic or secondary thrombocytopenia, acquired hemolytic anemia), gastrointestinal diseases (ulcerative colitis, regional enteritis) and edematous states.[10] Intraoral disorders for which steroids are indicated include recurrent aphthous stomatitis,[29] lichen planus,[30-32] pemphigus,[33] and pemphigoid.[30,33]

Table 4. Systemic equivalents for steroid medications

Generic Name	Milligrams[39]
Cortisone	25.00
Hydrocortisone	20.00
Prednisone	5.00
Methylprednisone	4.00
Triamcinolone	4.00
Dexamethasone	0.75

Table 5. Relative levels of potency of topical steroids[39]

Potency Level	Steroid (% Active Ingredient)
Ultra-potent	• Clobetasterol propionate (0.05%) • Halobetasterol propionate (0.05%)
Potent	• Desoximetasone (0.25%) • Fluocinonide (0.05%)
Moderately potent	• Betamethasone dipropionate (0.05%) • Betamethasone valerate (0.10%) • Fluticasone propionate (0.05%) • Triamcinolone acetonide (0.05%, 0.10%)
Mildly potent	• Aclometasone dipropionate (0.05%) • Hydrocortisone (0.05%, 0.10%)

Dental management of patients receiving steroid therapy. The mainstay of pharmacologic immunomodulation depends on the proper incorporation of steroid therapy into the management of many intraoral mucosal disorders such as recurrent aphthous ulcerations and lichen planus. This class of medications can be used either topically or systemically, but care must be exercised to minimize steroid-induced side effects. The medical history must be used to identify patients on chronic steroid therapy to manage systemic illness, to ensure that they can respond to the pain and anxiety of the dental procedure. The primary endogenously secreted glucocorticoid is cortisol. Cortisol and its exogenous analogues are responsible for a wide variety of functions and physiologic effects, which include the inhibition of inflammation. The anti-inflammatory action of cortisol is modulated by its inhibitory action on lysosome release, prostaglandin production, eicosanoid and cytokine release, endothelial cell expression of intracellular and extracellular adhesion molecules that attract neutrophils and the function of leukocytes.[34] Inappropriate management of patients on chronic steroid therapy could result in unusual but documented acute adrenal insufficiency (Addisonian crisis), which is potentially life threatening.[35,36] Because of the profound and varied metabolic effects caused by steroids, care must be taken in their administration.

Most adverse reactions to corticosteroids occur after a 2-week period.[37] Therefore, if systemic steroids are prescribed by the dentist, whenever possible, the general rule is to prescribe a higher dose for a short period of time (burst therapy) rather than a lower dose over a protracted period of time. Topical steroid therapy for oral mucosal disorders has been reported to be quite safe for a short-term course of therapy. Table 4 identifies systemic equivalent doses for steroids to assist the clinician in the prescription of these medications. If ultra-potency topical steroids are used (Table 5), there is a potential for systemic absorption. Custom trays and adhesive vehicles can be used to enhance the topical effect of intraorally applied topical steroids.[38]

There are no uniformly accepted or absolute guidelines for steroid supplementation in the dental setting. Current evidence suggests that most patients who are managed with chronic corticosteroids and undergoing routine dental therapy do not require supplementation as long as pain and anxiety are well controlled (Table 6).[35,40] However, patients on chronic corticosteroid therapy may remain at risk for adrenal suppression. Medical consultation with the patient's physician will assist the dental practitioner in determining if a need for steroid supplementation exists.

Conclusion

High-dose cytotoxic agents continue to be a key component of cancer treatment regimens directed to metastatic cancer. Despite development of medications that have shown impressive clinical outcomes in recent years, many of these products can directly impair immune function as well as wound healing. In addition, novel molecularly targeted therapies are being used with increasing frequency in oncology practice, with associated changes in toxicity profiles for many patients. Further research is needed in order to more fully define the adverse events associated with these molecules.

Table 6. Steroid supplementation guidelines for dental patients

Procedure	Guidelines[35,40]
Routine dental procedures including extractions managed with local anesthesia where pain can be well controlled both intraoperatively and postoperatively.	• Steroid supplementation is not usually necessary if the patient is currently taking steroids. Ensure effective local anesthesia and adequate postoperative pain control. • Administer normal maintainence steroid dose on the day of the procedure if patient has discontinued regular steroid usage within the previous 2-week period. • No supplementation is generally required if the patient has a previous history of regular steroid usage which has been discontinued for greater than 2 weeks or is using topical or inhalation steroids.
Extremely anxious patient managed with local anesthesia only Complicated or emotionally stressful procedure managed with local anesthesia only	• Double the patient's steroid regimen on the day of the procedure and the day after the procedure (if significant postoperative pain is anticipated) for patients currently taking steroids. • Double the normal maintainence dose on the day of the procedure if the patient has discontinued regular steroid usage within the previous 2-week period. • No supplementation is generally required if the patient has a previous history of regular steroid usage which has been discontinued for greater than 2 weeks.
Dental procedures requiring general anesthesia (usually in a hospital setting or outpatient surgical center	• Administer parenteral corticosteroids in a hospital setting using 100 mg hydrocortisone 1 hour before procedure and double the daily dose on the following day (if postoperative pain is anticipated).
Alternate day steroid regimen	• Treat patient on the day they normally take their steroid medication. No change in the steroid regimen is necessary.

It is essential that the dentist collaborate with the rest of the oncology team in order to prevent or ameliorate acute and chronic oral sequelae of antineoplastic therapies. This collaboration is warranted by compelling evidence in the literature, which suggests that high-risk oral lesions — of the dentition, periodontium, periradicular region, and mucosa — should be eliminated prior to initiation of myelosuppressive chemotherapy. In addition, chemotherapy can cause acute oral complications that in selected cases require several months following cessation of the drugs for clinical resolution. Multiprofessional approaches to management of these medically complex cancer patients can directly improve quality of life and, in some cases, patient survival.

Bisphosphonates (intravenous and oral) are used in management of osteoporosis, and osteoporosis-related sequelae of selected medications (e.g., anti-cancer, antipsychotic, antacids). Dental management should proceed with caution in patients currently taking this family of medications.

The mainstay of pharmacologic immunomodulation depends on the proper incorporation of steroid therapy into the management of many intraoral mucosal disorders such as recurrent aphthous ulcerations and lichen planus. This class of medications can be used either topically or systemically, but care must be exercised to minimize steroid-induced side effects. Proper use of this class of medications can significantly improve the morbitity of vesiculubullous and ulcerative oral mucosal disorders.

Disclosures

Douglas E. Peterson, DMD, PhD serves as consultant to Endo Pharmaceuticals, Genzyme Corporation, MGI Pharma, and Nuvelo.

Jon B. Suzuki, DDS, PhD, MBA serves on the scientific advisory boards of Biohorizons and Philips Oral HealthCare.

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