Dental Management of Pediatric Patients Receiving Immunosuppressive Therapy and/or Head and Neck Radiation

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Abstract

This best practice provides recommendations for oral health care for children undergoing immunosuppressive therapy and/or head and neck radiation. These children have unique oral health needs and are at risk of developing multiple associated oral and systemic complications. Dentists play an essential role in diagnosing, preventing, stabilizing, and treating oral health problems that can compromise a patient's quality of life before, during, and following such therapies. All children undergoing immunosuppressive therapy and/or head and neck radiation should have an oral examination before such treatment commences. Dental interventions must be performed promptly, efficiently, and with attention to the patient's unique circumstances and treatment protocol. Preventing new dental problems and treating existing dental conditions before immunosuppressive therapy and/or head and neck radiation is paramount. Preventive strategies include oral hygiene, diet, fluoride, and patient education. When completing all dental care prior to therapy is not feasible, priorities should be treatment of odontogenic and periodontal infections, extractions, periodontal care, and removal of sources of tissue irritation. Recommendations for management of caries lesions, pulp therapy, orthodontia, periodontal conditions, and extractions are included. Strategies to manage oral conditions related to immunosuppressive therapies and head and neck radiation are addressed. For children undergoing hematopoietic stem cell transplantation, all dental treatment should be completed before the patient becomes immunosuppressed and elective care postponed until immunological recovery has occurred.

This document was developed through a collaborative effort of the American Academy of Pediatric Dentistry Councils on Clinical Affairs and Scientific Affairs to offer updated information and guidance regarding dental management of pediatric patients receiving immunosuppressive therapy and/or head and neck radiation.

KEYWORDS: DENTAL CARE; IMMUNOSUPPRESSION; MUCOSITIS; PHOTOBIOMODULATION; RADIATION THERAPY; TREATMENT PROTOCOL

Purpose

The American Academy of Pediatric Dentistry (AAPD) recognizes that the pediatric dental professional plays an important role in the diagnosis, prevention, stabilization, and treatment of oral and dental problems that can compromise the child's quality of life before, during, and after immunosuppressive therapy and/or head and neck radiation. Immunosuppression may be the intended goal of therapies to prevent rejection of a donor organ or hematopoietic stem cell transplantation (**HSCT**), or it may be a consequence of anti-neoplastic chemotherapy or HSCT conditioning. Children undergoing such therapies will benefit from dental interventions that are prompt, efficient, and modified according to the patient's medical history, cancer treatment protocol, and health status.

Immunosuppressive therapy and/or head and neck radiation can cause many acute and long-term side effects in the oral cavity. Furthermore, any existing or potential sources of oral/dental infections and/or soft tissue trauma can compromise medical treatment, leading to greater morbidity and mortality, as well as higher hospitalization costs. It is imperative that the pediatric dentist be familiar with the patient's medical history and associated oral manifestations and appropriately address dental concerns in conjunction with the patient's medical team.

Methods

Developed by the Clinical Affairs Committee and adopted in 1986,[1] this best practice was last revised in 2022.[2] This revision by the Council on Clinical Affairs is based upon a review of current dental and medical literature related to immunosuppressive therapy, head and neck radiation, and best current practice. It included a new literature search of the

ABBREVIATIONS
ANC: Absolute neutrophil count. **CBC:** Complete blood count. **GVHD:** Graft versus host disease. **HSCT:** Hematopoietic stem cell transplantation. **Majr:** Medical subject heading major topic. **MRONJ:** Medication-related osteonecrosis of the jaw. **OM:** Oral mucositis. **PBM:** Photobiomodulation. **Tiab:** Title and abstract.

* *Used in the PubMed search to identify all terms that begin with this truncated base.*

PubMed/MEDLINE database using the terms: (*evidence based dentistry* [**Majr**] OR *pediatric dentistry* [Majr] OR *dental care for children* [Majr] OR *paediatric dentistry* [**Tiab**] OR *dental health services* [Majr] OR *dentistry* [Majr] OR *public health dentistry* [Majr] OR *community dentistry* [Majr]) AND (*oral health* [Majr] OR ***ANC*** [Tiab] OR *absolute neutrophil count* [Tiab] OR *blood cell count* [Majr] OR ***CBC*** [Tiab] OR *complete blood count* [Tiab] OR ***GVHD*** [Tiab] OR *graft versus host disease* [Tiab] OR *medication-related osteonecrosis* [Tiab] OR ***MRONJ*** [Tiab] OR *stomatitis* [Majr] OR *low-level light therapy* [Majr] OR *pediatric cancer** OR *pediatric oncology* [Tiab] OR *hematopoietic cell transplantation** OR *bone marrow transplantation** OR *immunosuppressive therap** OR *chemotherap** OR *radiotherap**); field: all; limits: within the last 10 years, clinical trial, practice guideline, randomized controlled trial, systematic review, meta-analysis, English, birth through age 18. One hundred sixty-four articles matched these criteria. Articles were reviewed by title and abstract, and 6 papers were chosen for full review. Additional papers for review were chosen from the references within selected articles. When data did not appear sufficient or were inconclusive, recommendations for additional reference papers were based upon expert and/or consensus opinion by experienced researchers and clinicians.

Background

A multidisciplinary approach involving physicians, nurses, dentists, social workers, dieticians, and other related health professionals is essential to care for the child before, during and after immunosuppressive therapy and/or head and neck radiation.[3,4] Acute and chronic oral complications that may occur as sequelae of such therapies include oral mucositis (**OM**) and associated pain[5], bleeding, taste dysfunction, opportunistic infections (eg, candidiasis, herpes simplex virus), dental caries, dry mouth (eg, salivary gland dysfunction, xerostomia), neurotoxicity, mucosal fibrosis, gingival hypertrophy, osteoradionecrosis, medication-related osteonecrosis, soft tissue necrosis, trismus, craniofacial and dental developmental anomalies, and oral graft versus host disease (**GVHD**).[4,6-9] Advances in cancer care have led to the development of additional treatments including targeted therapy and immunotherapy (eg, checkpoint inhibitors, T-cell transfer therapy, immune system modulators, monoclonal antibodies).[10(p434)] Although once thought to be less toxic than traditional chemotherapy, these therapies carry their own side effects, with cutaneous toxicities being the most frequently observed.[11] The oral toxicities associated with targeted therapies, although less well described, differ significantly from chemotherapy or radiation-induced oral damage (eg, aphthous-like stomatitis).[11]

All patients undergoing immunosuppressive therapy and/or head and neck radiation should have an oral examination prior to initiation of treatment[3,4] to identify any existing or potential source of oral disease or infection that may complicate the patient's medical treatment.[12,13] Every patient requires an individualized management plan and consultation with the patient's physicians and, when necessary, other dental specialists before commencing dental care.[4] Additionally, the key to success in maintaining a healthy oral cavity during therapy is patient compliance. Educating both the child and the parents regarding potential acute and long-term side effects of cancer therapies is essential, as this knowledge may motivate patients to adhere to oral care protocols during medical treatment.[9,13,14(p1304),15,16(p1246)]

Recommendations

Dental and oral care before the initiation of immunosuppressive therapy or head and neck radiation

Objectives[15,17]

The objectives of a dental examination prior to initiating therapy are as follow.

- To identify and stabilize or eliminate existing and potential sources of infection and local irritants in the oral cavity without needlessly delaying the treatment or inducing complications
- To communicate with the medical team regarding the patient's oral health status, plan, and timing of treatment
- To educate the patient and parents about the importance of optimal oral care to minimize oral problems and discomfort before, during, and after treatment and additionally to educate the family about possible acute and long-term effects of the therapy on the oral cavity and the craniofacial complex

Initial evaluation

Medical history review: should include disease/condition (diagnosis, type, stage, and prognosis), details of the treatment protocol (surgery, chemotherapy regimen, total number of planned cycles, cycle interval and dates of last/next cycle, radiation site and dose, plans for HSCT), medications (including bisphosphonates and other bone modifying agents), allergies, surgeries, secondary medical diagnoses, hematological status (eg, complete blood count [CBC]), immunosuppression status, presence of an indwelling venous line/catheter, and contact information for the medical team/primary care physician(s).[4] For patients undergoing HSCT, additional details should include the type of transplant (autologous vs allogenic), HSCT source (bone marrow, peripheral stem cells, cord blood stem cells), matching status, donor, conditioning protocol, planned date of transplant, and GVHD prophylaxis measures.

Dental history review: includes information such as fluoride exposure, oral habits, trauma, symptomatic teeth, previous dental care, preventive practices, oral hygiene, and diet.

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

Preventive strategies

Oral hygiene: Brushing of the teeth and tongue 2 to 3 times daily should be performed with a regular soft nylon-bristled or

electric toothbrush, regardless of hematological status.[4,14(p1304),16(p1245),18] Ultrasonic brushes and dental floss are recommended only if the patient is properly trained.[16(p1245)] If able, the patient should gently floss daily. If flossing results in pain or excessive bleeding, the patient should avoid the affected area but floss the other teeth.[4] Patients with poor oral hygiene and/or periodontal disease may use chlorhexidine rinses until the tissue health improves or mucositis develops.[13,19] The high alcohol content of commercially-available chlorhexidine mouthwash may cause discomfort and dehydrate the tissues in patients with mucositis. An alcohol-free chlorhexidine solution is indicated in this situation.

Diet: Dental practitioners should discuss the importance of a healthy diet to maintain nutritional status and emphasize non-cariogenic food choices. Patients and their parents should be advised about the high cariogenic potential of carbohydrate-rich dietary supplements and sucrose-sweetened medications.[20,21] They should also be instructed that sharp, crunchy, spicy, and highly-acidic foods and alcohol should be avoided during chemotherapy, head and neck radiation, and HSCT.[4]

Fluoride: Preventive measures include the use of fluoridated toothpaste, fluoride supplements if indicated, neutral fluoride gels/rinses, or applications of fluoride varnish for patients at risk for caries and/or dry mouth. A brush-on technique is convenient and may increase the likelihood of patient compliance with topical fluoride therapy.[16(p1245)]

Lip care: Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products.[4,22]

Trismus prevention/treatment: Patients who receive head and neck radiation may develop trismus. Daily oral stretching exercises and physical therapy should start before radiation is initiated and continue throughout treatment.[14(p1306),23]

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

Education: Patient and parent education includes the importance of optimal oral care in order to minimize oral problems and discomfort before, during, and after treatment and the potential acute and long-term effects of the therapy in the craniofacial complex.[4,19]

Dental care

Hematologic status: Dental providers should be aware of the patient's hematologic status and associated risks of bacteremia and excessive bleeding. Hematologic management of the patient should be directed by the patient's oncologist, and consultation with the medical team is necessary to determine the need for prophylactic interventions prior to dental treatment.

Immunosuppressed patients may be unable to tolerate a transient bacteremia following invasive dental procedures. Decisions regarding the need for antibiotic prophylaxis prior to dental treatment should be made in consultation with the child's physician. Unless advised otherwise, the American Heart Association's standard regimen to prevent endocarditis is an acceptable option for the immunocompromised patient.[4,24] The following parameters may be used to guide decisions on antibiotic prophylaxis.

- Absolute neutrophil count (ANC)
  - — >2,000/mm^3: Antibiotic prophylaxis is not necessary.[4,10(p442)]
  - — 1,000/mm^3 to 2,000/mm^3: Clinical judgment based on the patient's health status and planned procedures is indicated. Some authors[4] recommend antibiotic coverage when the absolute neutrophil count is within this range. If infection is present at the site of the planned procedure, a more aggressive prophylactic antibiotic therapy regimen may be discussed with the medical team.
  - — < 1,000/mm^3: Elective dental care should be deferred.[7,25] In dental emergencies, discussion with the medical team whether to manage with a course of antibiotic therapy versus a single dose of antibiotics for prophylactic coverage is indicated before proceeding with treatment.

Patients undergoing cancer treatments are at risk for thrombocytopenia. The following parameters may be used to determine need for pre- and postoperative interventions.

- Platelet count
  - — Although a platelet count of >60,000/mm^3 has been the threshold recommended by the American Academy of Pediatric Dentistry in recent guidance,[2,26(p407)] other published resources[10(p441),27] suggest invasive dental procedures may be performed with platelet counts in the 40,000-50,000/mm^3 range in selected cases, depending on the procedure and the patient's overall bleeding risk. When the platelets are below this range, elective treatment should be deferred and invasive procedures avoided when possible. When medically-necessary dental treatment is required, a hospital setting is most appropriate. Supportive measures (eg, platelet transfusions pre- and postoperatively, bleeding control, hospital admission and care) should be discussed with the patient's physician before proceeding. Localized hemostatic measures (eg, sutures, hemostatic agents, pressure packs, microfibrillar collagen, topical thrombin and/or gelatin foams) may be utilized to manage prolonged bleeding. Systemic measures such as aminocaproic acid and tranexamic acid may be recommended by the hematologist/oncologist. In cases of platelet

transfusions, the dentist should consult with the hematologist to determine the need for a posttransfusion platelet count before beginning dental treatment. Additional platelet transfusions should be available in the event of excessive and persistent intraoperative or postoperative bleeding.[27]

- Other coagulation tests may be necessary for individual patients.

Dental procedures: Ideally, all dental care should be completed before immunosuppressive and/or radiation therapy is initiated. If this is not feasible, temporary restorations may be placed and nonacute dental treatment may be delayed until the patient's hematological status is stable.[4,28] The patient's blood counts typically start falling 5 to 7 days after the beginning of treatment cycle and stay low for approximately 14 to 21 days before rising again to normal levels.

- Prioritizing procedures: When definitive dental care would delay oncologic treatment and negatively impact medical prognosis, providers may elect to prioritize treating symptomatic or potentially symptomatic conditions. This includes addressing caries lesions at risk of irreversible pulpitis, infections, and hopeless teeth (eg, root tips, nonrestorable teeth) and removing sources of tissue irritation before the treatment of asymptomatic carious teeth (eg, incipient, small asymptomatic caries lesions), root canal therapy for asymptomatic permanent teeth, and replacement of faulty restorations.[7,10(p442),28] Awareness that immunosuppressed patients may exhibit reduced signs and symptoms of periodontal disease and infection is important.[10(p450),14(p1308)]
- Pulp therapy in primary teeth: Few studies exist on the safety of performing pulp therapy in primary teeth prior to the initiation of chemotherapy and/or head and neck radiation. Many clinicians choose to extract pulpally-involved carious teeth due to the risk of becoming life-threatening during periods of immunosuppression.[16(p1243)] Asymptomatic teeth that are already pulpally treated and are clinically and radiographically sound should be monitored periodically for clinical and radiographic signs of failure.
- Endodontic treatment in permanent teeth: Symptomatic nonvital permanent teeth ideally should receive root canal treatment in a single visit at least 1 week before initiation of immunosuppressive therapy to allow time to assess treatment success.[7] If not possible, alternatives include pulpectomy and closure with an antibacterial agent or an extraction. The need for antibiotics is determined by the patient's health status and should be discussed with the patient's physician. Endodontic treatment of asymptomatic nonvital permanent teeth can be delayed until the immunologic status of the patient is stable.[7,10(p442)] The etiology of periapical radiolucencies associated with teeth previously treated endodontically should be determined as they may represent pulpal infections, inflammatory reactions, apical scars, cysts, or malignancies.[16(p1244)] Asymptomatic periapical lesions most likely depict apical scars and do not need retreatment.[28]
- Orthodontic appliances and space maintainers: Poorly-fitting appliances can result in a breach of oral mucosa and increased the risk of microbial invasion into deeper tissues.[25] Fixed appliances should be removed if the patient has poor oral hygiene or if the treatment protocol (eg, HSCT conditioning regimen, head and neck radiation) risks causing moderate to severe mucositis.[7,16(p1244)] Simple appliances (eg, band and loops, fixed lower lingual arches) that are not irritating to the soft tissues may be left in place in patients with good oral hygiene.[7,16(p1244)] Removable appliances and retainers that fit well may be worn as long as tolerated by the patient with good oral care.[16(p1244)] Patients should be instructed to clean their appliance daily and routinely clean appliance cases with an antimicrobial solution to prevent contamination and reduce the risk of appliance-associated oral infections. Removing orthodontic bands or adjusting prostheses that approximate gingival tissue is recommended if a patient is expected to receive cyclosporine or other drugs known to cause gingival hyperplasia. If band removal is not possible, vinyl mouth guards or orthodontic wax may be used to decrease tissue trauma.[16(p1244)]
- Periodontal considerations: Extraction is the recommended treatment for teeth with poor prognosis (eg, nonrestorable teeth, periodontal pockets >5 mm, significant bone loss, furcation involvement, mobility, infection) when definitive periodontal therapy is not possible.[16(p1244)] Partially-erupted molars can become a source of infection due to pericoronitis. If overlying gingival tissue is deemed a potential risk and the patient's hematological status permits, excision is recommended.[10(p442)]
- Third molars and other impacted teeth: Some practitioners prefer to extract all third molars that are not fully erupted, particularly prior to HSCT. Others favor a more conservative approach and only recommend extraction of third molars at risk for pulpal infection; with significant pathology, infection, periodontal disease, or pericoronitis; or when malposed or nonfunctional.[16(p1244),29]
- Primary teeth that are mobile due to natural exfoliation may be left alone.
- Extractions: Surgical procedures need to be as atraumatic as possible, ensuring no sharp bony edges remain and wounds are satisfactorily closed. Ideally, these extractions are performed 2 weeks before the initiation of cancer therapy to allow for adequate healing.[10(p442),16(p1244)] If the patient is immunocompromised and at risk for infection from transient bacteremia, consultation with the patient's physician regarding antibiotic prophylaxis is recommended. Regardless of hematologic status, if there is documented infection associated with the extracted tooth, antibiotics (ideally chosen with the benefit of sensitivity testing) should be administered for about 1 week postoperatively.[10(p450)]

- Pediatric patients receiving bone modifying agents (eg, bisphosphonates, antiresorptive agents, anti-angiogenic agents) as part of their cancer treatment or having had head and neck radiation are at an increased risk for medication-related osteonecrosis of the jaw (MRONJ) or osteoradionecrosis, respectively.[14(p1306),30-33] To minimize the risk for development of MRONJ or osteoradionecrosis, all oral surgical procedures (eg, extractions, periodontal treatment) should ideally be completed before these therapies begin.[31,32] Although evidence of MRONJ primarily has been described in the adult population,[31] there is risk of occurrence in pediatric patients. Those deemed to be at a significant risk for MRONJ or osteoradionecrosis who require oral surgery or an invasive periodontal procedure are best managed collaboratively by a dentist and the medical team in a hospital setting. Risks of osteonecrosis should be discussed with the patient and caregivers prior to proceeding.

Communication: Communication between the dentist and the medical team regarding the comprehensive oral care plan is vital. Information to be shared includes the extent of nonelective dental treatment required, the need for supportive care (eg, hospital admission, blood product replacement, antibiotic coverage), and the time needed for stabilization of oral disease and healing post dental procedures. These discussions help facilitate coordination between essential dental services and planned cancer therapy.[4]

Oral care during immunosuppression periods and radiation therapy

Preventive strategies

Maintaining good oral hygiene in patients undergoing immunosuppressive therapy and head and neck radiation is necessary to reduce the microbial load in the oral cavity. This may decrease the host inflammatory response and subsequent severity of OM. Furthermore, a clean oral cavity reduces the risk for opportunistic infections.[4,10(p442),13,14(p1308),16(p1249),18,25] Patients should continue to use a soft nylon brush 2 to 3 times daily and replace it every 2 to 3 months.[16(p1245),18]

Thrombocytopenia is not the sole determinant of oral hygiene as patients are able to brush without bleeding at widely different levels of platelet counts.[16(p1245)] Fluoridated toothpaste is effective for caries prevention, and a mildly-flavored toothpaste may be better tolerated during periods of OM. If moderate to severe OM develops and the patient cannot tolerate a regular soft nylon toothbrush or an end-tufted brush, foam brushes or super soft brushes soaked in chlorhexidine may be used.[15,17] However, foam or super soft brushes typically are discouraged because they do not allow for effective cleaning. The use of a regular brush should be resumed once the OM improves.[16(p1245),18] Brushes should be air-dried between uses.[16(p1245)] Electric or ultrasonic brushes are acceptable if the patient can use them without causing trauma and irritation. If patients can floss without traumatizing the tissues, flossing may continue throughout treatment. Toothpicks and water irrigation devices should not be used when the patient is pancytopenic to prevent tissue trauma.[16(p1251)]

Dental care

During immunosuppression, elective dental care should be deferred. In the event of a dental emergency, consultation with the patient's physician regarding the treatment plan is recommended to determine the need for supportive medical therapies (eg, antibiotics, platelet transfusions, analgesia). The patient's oral health should be reevaluated every 6 months (or in shorter intervals if there is a risk for dry mouth, caries, trismus, and/or chronic oral GVHD) during treatment, in times of stable hematological status, and always after reviewing the medical history.

Management of oral mucositis and associated pain related to immunosuppressive therapies

Oral mucositis: Oral mucositis is a frequent adverse effect of antineoplastic chemotherapy and/or high-dose head and neck radiation and HSCT. Characterized by erythema and ulceration of the oral mucosa, it leads to pain and inability to eat and, when severe, may interrupt cancer therapy. More recently, aphthous-like ulcerations also have been recognized as toxicities associated with targeted biologic therapies including mammalian target of rapamycin (mTOR) inhibitors (eg, temsirolimus and everolimus)[11,34] and immune checkpoint inhibitors targeting T-lymphocyte antigen 4[10(p434)], programmed death receptor-1 (PD-1)[11], and programmed death-ligand 1 (PD-L1)[10(p434),11].

The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published guidelines for treatment of OM.[18,35] Currently, data for the pediatric population is limited; thus, recommendations are based largely on adult studies. The recommended prescriptions for prevention of OM include patient education, good oral hygiene, bland mouth rinses (saline or sodium bicarbonate), benzydamine mouthrinse, cryotherapy, palifermin, and photobiomodulation therapy (**PBM**).[35-37] Mucosal coating agents (eg, hydroxypropylmethylcellulose) and film-forming agents also have been suggested.[4] The use of sucralfate, antimicrobial lozenges, chlorhexidine, pentoxifylline, and granulocyte-macrophage colony stimulating factor mouthwash for OM are not recommended.[18,19,35]

Oral cryotherapy, the cooling of intraoral tissue with ice, is recommended as OM prophylaxis for patients receiving bolus infusion of chemotherapy drugs with short half-lives.[35,38] Oral cryotherapy reduces the blood flow to the mouth by constricting the blood vessels, thus limiting the amount of chemotherapy drugs delivered to the tissues. Cryotherapy is inexpensive and readily available, but further research is needed to confirm the effectiveness of oral cryotherapy in children.[36,38]

Palifermin (keratinocyte growth factor-1) is approved by the US Food and Drug Administration for the prevention of OM[39] in patients undergoing conditioning with high-dose chemotherapy and total body irradiation followed by HSCT.[35]

Palifermin works by stimulating the reproduction, growth, and development of epithelial cells, quickly replacing mucosal cells damaged by chemotherapy and radiation and accelerating the healing process.[14(p1291),40] Due to the high cost, restricted availability, and potential negative short-term side effects (ie, rash, erythema, white-coated tongue) and long-term negative cancer outcomes (ie, squamous cell carcinoma), routine use of palifermin in the pediatric population is not recommended.[41]

The current Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology guidelines support the use of PBM therapy to prevent OM in patients undergoing HSCT conditioning with high-dose chemotherapy with or without total body irradiation as well as patients undergoing radiation treatment for head and neck cancer.[35,37,41] Intraoral PBM using a red light spectrum of 620-750 nm[41] can decrease pain and the duration and severity of chemotherapy-induced OM in children.[37,42-44] PBM may not be available at all cancer treatment centers due to the cost of the equipment and the need for trained personnel.[41] Appropriate protocol must be followed when using PBM to prevent contamination and occupational risks to the child and dental team.

Regarding chlorhexidine, most studies have not demonstrated a prophylactic impact or a reduction in the severity of OM.[10(p447),14(p1303),19,45,46] Chlorhexidine is not recommended for prevention of OM in patients undergoing head and neck radiation.[19,35]

Patient-controlled analgesia is helpful in relieving pain associated with OM, reducing the requirement for oral analgesics. The use of topical anesthetics and mixtures containing topical anesthetics (eg, Philadelphia mouthwash, magic mouthwash, 0.2% morphine mouthwash) has been suggested for pain management.[18,35,47] However, topical anesthetics only provide short-term pain relief.[18] In addition to possible cardiovascular and central nervous system effects, their use may obtund or diminish taste and the gag reflex[14(p1303)] and/or result in a burning sensation. Currently, the evidence for their benefit is lacking,[19] and potential for toxicity is a concern in young children.

Management of oral ulcerations and other oral toxicities that develop during immune-mediated therapy should focus on pain relief and accelerated healing of lesions.[48] Options include topically-delivered steroids either in a gel for single lesions (eg, triamcinolone 0.1% ointment) or a swish-and-spit solution for extensive involvement (eg, tacrolimus 0.1mg/mL, dexamethasone 0.1mg/mL).[11,48] Topical agents (eg, benzydamine hydrochloride 0.15%, viscous lidocaine 2%) may offer transient pain relief but can be challenging to deliver to the young patient.[48]

Oral dysesthesia: The focus of care is on symptom relief and management typically includes gamma-aminobutyric acid (GABA) analogs or topical or systemic benzodiazepines (eg, clonazepam).[48] Sensitivity or burning may be controlled with topical anesthetics.[48]

Oral mucosal infections: During neutropenic periods, the signs of oral mucosal inflammation and infection may be diminished, leading to an atypical clinical appearance.[10(p450)] Close monitoring of the oral cavity allows for timely diagnosis and treatment of fungal, viral, and bacterial infections. Oral cultures and/or biopsies of suspicious lesions or lesions that do not resolve after 14 days[10(p441)] are appropriate if medical status permits. While waiting for the results, empiric therapy typically is initiated until laboratory results dictate more specific medications.[4,10(p449),16(p1249)] Of note, nystatin is ineffective for both the prevention and/or treatment of fungal infections.[14(p1308),49]

Oral bleeding: Oral bleeding in patients undergoing immunosuppressive therapy commonly occurs due to thrombocytopenia and/or damaged vascular integrity. Management involves both local (eg, pressure packs, antifibrinolytic rinses or topical agents, gelatin sponges) and systemic (eg, platelet transfusions, aminocaproic acid) measures.[10(p450),14(p1310),16(p1251)]

Dental sensitivity/pain: Tooth sensitivity may be related to dry mouth during chemotherapy or reduced salivary pH during head and neck radiation therapy.[10(p450),14(p1304),16(p1251)] Patients who are using plant alkaloid chemotherapeutic agents (eg, vincristine, vinblastine) may experience neurotoxicity that presents as deep, constant jaw pain (affecting the mandibular molars with greater frequency) or as a paresthesia in the absence of odontogenic pathology. The pain usually is transient and generally subsides shortly after dose reduction and/or cessation of chemotherapy.[10(p450),14(p1304),16(p1252)]

Dry mouth: Sugar-free chewing gum or candy, sucking tablets, special dentifrices for oral dryness, saliva substitutes, frequent sipping of water, normal saline or alcohol-free oral rinses, and/or oral moisturizers are recommended.[6,14(p1304),16(p1251),50] Placing a humidifier by the child's bedside at night may be useful.[10(p432)] For caries prevention, fluoride rinses and gels are highly recommended.

Trismus: Daily oral stretching exercises and physical therapy should be implemented during head and neck radiation treatment to reduce the risk of trismus. Management of trismus may include prosthetic aids to reduce the severity of fibrosis, trigger-point injections, analgesics, muscle relaxants, and other pain management strategies.[14(p1306),25,51]

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation is used in children to treat malignancies and hematologic disorders, as well as certain metabolic syndromes. Examples include[52]

- malignant disorders treated with autologous HSCT.
  - brain tumors
  - Ewing sarcoma
  - germ cell tumors
  - Hodgkin lymphoma
  - leukemia

  - neuroblastoma
  - non-Hodgkin lymphoma
  - Wilms tumor
- malignant disorders treated with allogenic HSCT.
  - acute lymphocytic leukemia
  - acute myeloid leukemia
  - high-risk solid tumors
  - juvenile myelomonocytic leukemia
  - myelodysplastic syndrome
- nonmalignant disorders treated with allogenic HSCT.
  - bone marrow failure syndromes
  - chronic granulomatous disease
  - Fanconi anemia
  - metabolic storage disorders
  - osteopetrosis
  - severe aplastic anemia
  - sickle cell anemia
  - thalessemia
  - Wiskott-Aldrich syndrome

Specific oral complications can be correlated with different phases of HSCT.[3,4,7,13,18]

Phase I: Preconditioning
The oral complications during preconditioning stem from the patient's current systemic and oral health, manifestations of the underlying disease, and recent medical therapy. Oral complications include opportunistic infections, gingival leukemic infiltrates, bleeding, and ulceration.[4] Most of the principles of dental and oral care before the transplant are similar to those discussed for patients undergoing immunosuppressive cancer therapy.[15] The 2 major differences in HSCT versus antineoplastic chemotherapy alone are: 1) the patient receives extremely high dose chemotherapy and/or total body irradiation immediately prior to (a few days before) the transplant, and 2) there will be prolonged immunosuppression following the transplant. Immunologic recovery may be longer if chronic GVHD or other complications (eg, persistent immunodeficiency) are present.[16(p1249)] Due to these differences, all dental treatment ideally should be completed before the patient undergoes HSCT, and elective dentistry is not recommended until after immunological recovery, which occurs at least 100 days following HSCT.

Phase II: Conditioning and neutropenic phase
The conditioning and neutropenic phase typically spans from the day the patient is admitted to the hospital to begin the transplant conditioning to 30 days post-HSCT. The majority of oral complications in this phase arise from the conditioning regimen and supportive medical therapies.[16p1252] Patients may experience mucositis, dry mouth, oral pain, hemorrhage, opportunistic infections, taste dysfunction, neurotoxicity (including dental pain, muscle tremors), and temporomandibular dysfunction (including jaw pain, headache, joint pain).[4] Oral mucositis usually begins 7 to 10 days after initiation of conditioning, and symptoms continue approximately 2 weeks after its completion.[4] Among allogeneic HSCT patients, acute GVHD can occur and exacerbate inflammation and severe mucositis symptoms. Acute GVHD may appear as early as 2 to 3 weeks after HSCT initiation and continue for up to 2 months posttransplant.

The prolonged presentation beyond 2 to 3 weeks after conditioning may help distinguish acute GVHD from chemotherapy-induced OM.[4] Closely monitoring and managing the oral changes and reinforcing the importance of optimal oral care are advised. Elective dental procedures are avoided in this phase due to the patient's severe immunosuppression. If emergency dental treatment is necessary, the dentist should consult and coordinate with the transplant team.

Phase III: Engraftment to hematopoietic recovery
The intensity and severity of acute complications observed in Phase II usually decrease 3 to 4 weeks after transplantation. However, during this phase, acute GVHD can become a concern for allogeneic graft recipients. Additional complications such as dry mouth, hemorrhage, neurotoxicity, temporomandibular dysfunction, and papillomas may occur.[4] Opportunistic infections such as oral fungal infections and herpes simplex virus infection are more prevalent during this phase.[4] HSCT patients are particularly sensitive to intraoral thermal stimuli between 2 and 4 months posttransplant.[16(p1252)] The mechanism is not well understood, but the symptoms usually resolve spontaneously within a few months. Topical application of neutral fluoride or desensitizing toothpastes helps reduce the symptoms.[16(p1252)] Due to the patient's continued immunosuppression, dental/oral examinations can be performed; however, any invasive dental procedures, including dental cleanings and soft tissue curettage, should be avoided unless deemed necessary after consultation with the HSCT team.[16(p1255)] Patients should be encouraged to optimize oral hygiene and avoid a cariogenic diet.

Phase IV: Immune reconstitution/recovery from systemic toxicity
After day 100 post-HSCT, oral complications are mainly due to the chronic toxicity from the conditioning regimen. These include dry mouth, craniofacial growth abnormalities, late viral infections, and chronic oral GVHD.[4,16(p1254)] Unless the patient is neutropenic or with severe chronic GVHD, mucosal bacterial infections are less common. Periodic dental examinations with radiographs can be performed, but invasive dental treatment is to be avoided in patients with persistent profound immune function impairment.[16(p1255)] Consultation with the patient's physician and parents regarding the risks and benefits of orthodontic care is recommended.

Dental and oral care after immunosuppressive therapy and head and neck radiation have been completed
Objectives
The objectives of a dental/oral examination after the cessation of immunosuppressive therapy are to

- maintain optimal oral health.

- reinforce the importance of optimal oral and dental care for life.
- address any long-term dental issues arising from the immunosuppressive therapy or head and neck radiation.

Dental care

Periodic evaluation: The patient should be seen every 6 months or more frequently if issues such as chronic oral GVHD, dry mouth, or trismus are present. Patients who have experienced moderate or severe mucositis and/or chronic oral GVHD require close monitoring due to an increased risk for malignant transformation of their oral mucosa (eg, oral squamous cell carcinoma).[4,13,53] Patients who have received an organ transplant are best able to tolerate dental care at least 3 months after transplant when overall health improves.[3]

Education: The importance of optimal oral and dental care for life must be reinforced. It is also important to emphasize the need for regular follow-ups with a dental professional. This is especially true for patients at risk for or who have developed GVHD and/or dry mouth and those who were younger than 6 years of age during treatment due to potential dental developmental problems.

Orthodontic treatment: Orthodontic care may start or resume after completion of therapy and after at least a 2-year disease-free survival when the risk of relapse is decreased and the patient is no longer using immunosuppressive drugs.[7,54] A thorough assessment of any dental developmental disturbances caused by the therapy must be performed before initiating orthodontic treatment. The following strategies may be considered when providing orthodontic care for patients with dental sequelae: (1) use appliances that minimize the risk of root resorption, (2) use lighter forces, (3) terminate treatment earlier than normal, and (4) choose the simplest method for the treatment needs.[55] However, specific guidelines for orthodontic management, including optimal force and pace, remain undefined. Patients and their families may be made aware of the need for closer follow-up due to the higher risk of orthodontic relapse among cancer survivors.[57] Patients who were on intravenous antiresorptive or anti-angiogenic agents as part of their cancer treatment, or in those who have had head and neck radiation, may present a challenge for orthodontic care. Although bisphosphonate inhibition of tooth movement has been reported in animals, it has not been quantified for any dose or duration of therapy in humans.[55,57] Consultation with the patient's caregivers and physician regarding the risks (eg, prolonged treatment time, MRONJ, treatment modifications) and benefits (eg, reduced root resorption, anchorage, less relapse) of orthodontic care in this situation is recommended.[57]

Oral surgery and invasive periodontal therapy: Patients at risk for MRONJ or osteoradionecrosis should be managed in the hospital setting in coordination with the oncology team.[30-32] Elective invasive procedures are best avoided in these patients.[32,57]

Long-term concerns

Craniofacial, skeletal, and dental developmental issues are some of the complications faced by survivors[3,7,9,16(p1255)] and are more common among children who were less than 6 years of age at the time of their cancer therapy.[7,16(p1256)] Long-term effects of immunosuppressive therapy may include tooth agenesis, microdontia, crown disturbances (size, shape, enamel hypoplasia, pulp chamber anomalies), root disturbances (early apical closure, blunting, changes in shape or length), reduced mandibular length, reduced alveolar process height, and reduced vertical growth of the face.[6,7,9,14(p1306)] The severity of the dental developmental anomaly will depend on the age and stage of development during exposure to cytotoxic agents or ionizing radiation. Patients may experience permanent salivary gland hypofunction/dysfunction or dry mouth.[51] Relapse or secondary malignancies may develop.[4,53] Routine periodic examinations are necessary to provide comprehensive oral health care. Careful examination of extraoral and intraoral tissues (including clinical, radiographic, and/or additional diagnostic examinations) are integral to diagnosing any secondary malignancies in the head and neck region such as oral squamous cell carcinoma.[4] Dental treatment may require a multidisciplinary approach, involving a variety of dental specialists to address the treatment needs of each individual. Consultation with the patient's physician is recommended if relapse occurs or the patient's immunologic status declines.

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