

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

## Latest Revision

2022

**How to Cite:** American Academy of Pediatric Dentistry. Dental management of pediatric patients receiving immunosuppressive therapy and/or head and neck radiation. *The Reference Manual of Pediatric Dentistry*. Chicago, Ill.: American Academy of Pediatric Dentistry; 2024:545-53.

## 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 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; PHOTOBIMODULATION; 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 cell transplantation (HCT), or it may be a consequence of anti-neoplastic chemotherapy or HCT 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 may 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 as *Management of Pediatric Dental Patients Receiving Chemotherapy and/or Radiation* and adopted in 1986<sup>1</sup>, this best practice was last revised in 2018<sup>2</sup>. This revision is based upon a review of current dental and medical literature related to immunosuppressive therapy, head and neck radiation, and best current practice. The revision by the Council on Clinical Affairs included a new literature search of the PubMed®/MEDLINE database

## ABBREVIATIONS

**AAPD:** American Academy of Pediatric Dentistry. **ANC:** Absolute neutrophil count. **CBC:** Complete blood count. **GVHD:** Graft versus host disease. **HCT:** Hematopoietic cell transplantation. **MASCC/ISOO:** The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology. **/mm<sup>3</sup>:** Per cubic millimeter. **MRONJ:** Medication-related osteonecrosis of the jaw. **OM:** Oral mucositis. **PBM:** Photobiomodulation.

using the terms: pediatric cancer, pediatric oncology, hematopoietic cell transplantation, bone marrow transplantation, immunosuppressive therapy, mucositis, stomatitis, chemotherapy, radiotherapy, acute effects, long-term effects, dental care, oral health, pediatric dentistry, practice guideline; field: all; limits: within the last 10 years, humans, English, birth through age 18. Two thousand sixty-five articles matched these criteria. Ninety-five papers were chosen for review from this list and from the references within selected articles. When data did not appear sufficient or were inconclusive, recommendations 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.<sup>3,4</sup> Acute and chronic oral complications that may occur as sequelae of such therapies include oral mucositis (OM) and associated pain, bleeding, taste dysfunction, opportunistic infections (e.g., candidiasis, herpes simplex virus), dental caries, dry mouth (e.g., 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).<sup>4-8</sup>

All patients undergoing immunosuppressive therapy and/or head and neck radiation should have an oral examination prior to initiation of treatment<sup>3,4</sup> to identify any existing or potential source of oral disease or infection that may complicate the patient's medical treatment.<sup>9,10</sup> Every patient requires an individualized management approach. Consultations with the patient's physicians and, when appropriate, other dental specialists, should be sought before dental care is instituted.<sup>4</sup> Additionally, the key to success in maintaining a healthy oral cavity during therapy is patient compliance. Educating the child and the parents regarding the possible acute and long-term side effects of cancer therapies is essential, as this may improve patient motivation to adhere to oral care protocols during cancer therapy.<sup>8,10-13</sup>

## Recommendations

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

#### Objectives<sup>13,14</sup>

The objectives of a dental/oral examination before therapy starts are three-fold:

- 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 to inform them about the possible acute and long-term effects of the therapy in the oral cavity and the craniofacial complex.

#### Initial evaluation

Medical history review: should include disease/condition (type, stage, prognosis), treatment protocol (conditioning regimen, surgery, chemotherapy, location and dose of radiation), medications (including bisphosphonates and other bone modifying agents), allergies, surgeries, secondary medical diagnoses, hematological status (e.g. complete blood count [CBC]), immunosuppression status, presence of an indwelling venous access line, and contact of medical team/primary care physician(s).<sup>4</sup> For HCT patients, the type of transplant, HCT source (i.e., bone marrow, peripheral stem cells, cord blood stem cells), matching status, donor, conditioning protocol, expected date of transplant, and GVHD prophylaxis should be elicited.

Dental history review: includes information such as fluoride exposure, habits, trauma, symptomatic teeth, previous 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 two to three times daily should be performed with a regular soft nylon-bristled or electric toothbrush, regardless of hematological status.<sup>11,12,15,16</sup> Ultrasonic brushes and dental floss should only be allowed if the patient is properly trained.<sup>12</sup> If capable, the patient should gently floss daily. If pain or excessive bleeding occurs, the patient should avoid the affected area but floss the other teeth.<sup>4</sup> Patients with poor oral hygiene and/or periodontal disease may use chlorhexidine rinses until the tissue health improves or mucositis develops.<sup>10,17</sup> 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 food choices that do not promote caries. Patients and parents should be advised about the high cariogenic potential of carbohydrate-rich dietary supplements and sucrose-sweetened medications.<sup>18,19</sup> 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 HCT.<sup>4</sup>

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.<sup>12</sup>

Lip care: Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products.<sup>20</sup>

Trismus prevention/treatment: Patients who receive head and neck radiation may develop trismus. Thus, daily oral stretching exercises/physical therapy should start before radiation is initiated and continue throughout treatment.<sup>11,21</sup>

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 (e.g., three-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 possible acute and long-term effects of the therapy in the craniofacial complex.<sup>4,17</sup>

#### *Dental care*

Dental providers should be aware of the patient's hematologic status and related 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.

In particular, patients who are immunosuppressed may not be able to tolerate a transient bacteremia following invasive dental procedures. A decision 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.<sup>4,16</sup> The following parameters may be used to guide decisions regarding need for antibiotic prophylaxis:

- Absolute neutrophil count (ANC):
  - > 2,000 per cubic millimeter (/mm<sup>3</sup>): no need for antibiotic prophylaxis;<sup>4,21</sup>
  - 1,000 to 2,000/mm<sup>3</sup>: Use clinical judgment based on the patient's health status and planned procedures. Some authors<sup>4</sup> suggest that antibiotic coverage may be prescribed when the ANC is in 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; and

- < 1,000/mm<sup>3</sup>: defer elective dental care.<sup>7,22</sup> In dental emergencies, discuss management with a course of antibiotic therapy versus one dose of antibiotics for prophylactic coverage with the medical team 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:
  - < 60,000/mm<sup>3</sup>: Defer elective treatment and avoid invasive procedures when possible. When medically-necessary dental treatment is required, a hospital setting is most appropriate. Discuss supportive measures (e.g., platelet transfusions pre- and postoperatively, bleeding control, hospital admission and care) with the patient's physician before proceeding. Localized hemostatic measures to manage prolonged bleeding may be utilized (e.g., sutures, hemostatic agents, pressure packs, microfibrillar collagen, topical thrombin and/or gelatin foams). Systemic measures (e.g., aminocaproic acid, tranexamic acid) may be recommended by the hematologist/oncologist. If platelet transfusions are administered, the dentist should consult with the hematologist regarding the need for a posttransfusion platelet count before the commencement of dental treatment. Additional transfusions would ideally be available in the event of excessive and persistent intra-operative or postoperative bleeding.<sup>23</sup>
- Other coagulation tests may be in order for individual patients.

Dental procedures:

- Ideally, all dental care should be completed before immunosuppressive therapy is initiated. When that is not feasible, temporary restorations may be placed and non-acute dental treatment may be delayed until the patient's hematological status is stable.<sup>4,24</sup> The patient's blood counts typically start falling five to seven days after the beginning of treatment cycle and stay low for approximately 14 to 21 days before rising again to normal levels. Patients who require an organ transplant are best able to tolerate dental care at least three months after transplant when overall health improves.<sup>3</sup>
- Prioritizing procedures: In the event that definitive dental care would result in a delay of oncologic treatment and a resultant poorer medical prognosis, providers may prioritize treatment of symptomatic or potentially symptomatic caries lesions (risk of irreversible pulpitis), infections, hopeless teeth (e.g., root tips, nonrestorable teeth) and removal of sources of tissue irritation before the treatment of asymptomatic carious teeth (e.g., incipient, small asymptomatic caries lesions), root canal therapy for asymptomatic permanent teeth, and replacement of faulty restorations.<sup>7,21,24</sup> It is important for the practitioner

to be aware that the signs and symptoms of periodontal disease and infection may be decreased in immunosuppressed patients.<sup>11,21</sup>

- Pulp therapy in primary teeth: Few studies have evaluated 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 because of the potential for pulpal/periapical/furcal infections to become life-threatening during periods of immunosuppression.<sup>12</sup> 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 one week before initiation of immunosuppressive therapy to allow sufficient time to assess treatment success.<sup>7,21</sup> If that is not possible, alternative options include pulpectomy and closure with an antibacterial agent or 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 may be delayed until the immunologic status of the patient is stable.<sup>7,21</sup> The etiology of periapical radiolucencies associated with teeth previously treated endodontically should be determined because they may represent pulpal infections, inflammatory reactions, apical scars, cysts, or malignancies.<sup>12</sup> Periapical lesions that are asymptomatic and most likely depict apical scars do not need retreatment.<sup>24</sup>
- 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.<sup>22</sup> Fixed appliances should be removed if the patient has poor oral hygiene or if the treatment protocol (e.g., HCT conditioning regimen, head and neck radiation) carries a risk for the development of moderate to severe mucositis.<sup>7</sup> Simple appliances (e.g., band and loops, fixed lower lingual arches) that are not irritating to the soft tissues may be left in place in patients with good oral hygiene.<sup>7,12</sup> Removable appliances and retainers that fit well may be worn as long as tolerated by the patient with good oral care.<sup>12</sup> 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. Consider removing orthodontic bands or adjusting prostheses that approximate gingival tissue 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 should be used to decrease tissue trauma.<sup>12</sup>
- Periodontal considerations: Extraction is the treatment of choice for teeth with a poor prognosis (e.g., nonrestorable teeth, periodontal pockets greater than five millimeters, significant bone loss, furcation involvement, mobility, infection) that cannot be treated by definitive periodontal therapy. Partially-erupted molars can become a source of infection because of pericoronitis. The overlying gingival tissue should be excised if the dentist believes it is a potential risk and if the hematological status permits.<sup>12,21</sup>
- Third molars and other impacted teeth: Some practitioners prefer to extract all third molars that are not fully erupted, particularly prior to HCT. 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.<sup>12,25,26</sup>
- Primary teeth that are mobile due to natural exfoliation may be left alone.
- Extractions: Surgical procedures must be as atraumatic as possible, with no sharp bony edges remaining and satisfactory closure of the wounds. These extractions ideally are performed three weeks (or at least 10 to 14 days) before cancer therapy is initiated to allow for adequate healing.<sup>12,21</sup> If the patient is immunocompromised and at risk of infection from transient bacteremia, antibiotic prophylaxis should be discussed with the patient's physicians. 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 one week post-operatively.<sup>12,21</sup>
- Pediatric patients who are on bone modifying agents (e.g., bisphosphonates, antiresorptive agents, anti-angiogenic agents) as part of their cancer treatment or who have had head and neck radiation are at an increased risk of medication-related osteonecrosis of the jaw (MRONJ) or osteoradionecrosis<sup>27-30</sup>, although most of the evidence has been described in the adult population<sup>28</sup>. Patients deemed to be at a significant risk of MRONJ or osteoradionecrosis are best managed by a dentist in coordination with the medical team in a hospital setting. To minimize the risk of development of osteoradionecrosis or MRONJ, patients ideally would have all oral surgical procedures (e.g., extractions, periodontal treatment) completed before those therapies are instituted.<sup>27,28</sup> For patients who have been on antiresorptive (e.g., bisphosphates, denosumab) or anti-angiogenic agents as part of their cancer treatment or have had radiation to the jaws and an oral surgical procedure or invasive periodontal procedure is necessary, it is important to discuss risks with the patient and caregivers prior to the procedure.

#### Communication:

The dentist's communication of the comprehensive oral care plan with the medical team is vital. Information to be shared

includes the extent of non-elective dental treatment needed, need for supportive care (e.g., hospital admission, blood product replacement, antibiotic coverage) and the amount of time needed for stabilization of oral disease and healing from the dental procedures. Discussions with the medical team can ensure ideal coordination between needed dental services and planned cancer therapy.<sup>4</sup>

### **Oral care during immunosuppression periods and radiation therapy**

#### *Preventive strategies*

**Oral hygiene:** Maintenance of good oral care 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 of opportunistic infections.<sup>4,10-12,15,21,22</sup> Patients should use a soft nylon brush two to three times daily and replace it every two to three months.<sup>12,15</sup>

Thrombocytopenia is not the sole determinant of oral hygiene as patients are able to brush without bleeding at widely different levels of platelet counts.<sup>12</sup> 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.<sup>13,14</sup> Otherwise, foam or super soft brushes are discouraged because they do not allow for effective cleaning. The use of a regular brush should be resumed as soon as the OM improves.<sup>12,15</sup> Brushes should be air-dried between uses.<sup>12</sup> Electric or ultrasonic brushes are acceptable if the patient can use them without causing trauma and irritation. If patients are skilled at flossing without traumatizing the tissues, it is reasonable to continue flossing throughout treatment. Toothpicks and water irrigation devices should not be used when the patient is pancytopenic to avoid tissue trauma.<sup>12</sup>

#### *Dental care*

During immunosuppression, elective dental care should be deferred. If a dental emergency arises, the treatment plan should be discussed with the patient's physician who will make recommendations for supportive medical therapies (e.g., antibiotics, platelet transfusions, analgesia). The patient's oral health should be reevaluated every six months (or in shorter intervals if there is a risk of 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:** The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published guidelines for treatment of

OM.<sup>15,31</sup> Currently, data for the pediatric population is limited; thus, recommendations are based largely on adult studies. The recommended prescriptions for prevention of OM include good oral hygiene, bland mouth rinses (saline or sodium bicarbonate), benzydamine mouthrinse, cryotherapy, palifermin, and photobiomodulation therapy (PBM).<sup>31,32</sup> Mucosal coating agents (e.g., hydroxypropylmethylcellulose) and film-forming agents also have been suggested.<sup>4</sup> The use of sucralfate, antimicrobial lozenges, chlorhexidine, pentoxifylline, and granulocyte-macrophage colony stimulating factor mouthwash for OM are not recommended.<sup>15,31</sup>

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.<sup>31,33</sup> Oral cryotherapy reduces the blood flow to the mouth by narrowing 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.<sup>32,33</sup>

Palifermin (keratinocyte growth factor-1) is a drug approved by the United States Food and Drug Administration for the prevention of oral mucositis<sup>34</sup> in patients undergoing conditioning with high-dose chemotherapy and total body irradiation followed by HCT.<sup>31</sup> Palifermin exerts its effect by stimulating epithelial cell reproduction, growth, and development so that mucosal cells damaged by chemotherapy and radiation are replaced quickly, accelerating the healing process.<sup>11,35</sup>

The current MASCC/ISOO guidelines support the use of PBM therapy to prevent OM in patients undergoing HCT conditioning with high-dose chemotherapy with or without total body irradiation as well as patients undergoing radiation treatment for head and neck cancer.<sup>31</sup> PBM can decrease pain and the duration and severity of chemotherapy-induced OM in children.<sup>36-38</sup> PBM may not be available at all cancer treatment centers due to the cost of the equipment and the need for trained personnel. Appropriate protocol must be followed when using PBM to prevent contamination and occupational risks to the child and dental team.

With regard to chlorhexidine, most studies have not demonstrated a prophylactic impact or a reduction in the severity of OM.<sup>11,21,39,40</sup> Chlorhexidine is not recommended for prevention of oral mucositis in patients undergoing head and neck radiation.<sup>15,31</sup>

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 (e.g., Philadelphia mouthwash, magic mouthwash) has been suggested for pain management.<sup>15,41</sup> However, topical anesthetics only provide short-term pain relief.<sup>15</sup> In addition to possible cardiovascular and central nervous system effects, their use may obtund or diminish taste and the gag reflex<sup>11</sup> and/or result in a burning sensation. Currently, the evidence for their benefit is lacking<sup>17</sup>, and potential for toxicity is a concern in young children.

Oral mucosal infections: The signs of oral mucosal inflammation and infection may be diminished during neutropenic periods. Thus, the clinical appearance of infections may differ significantly from the expected.<sup>21</sup> Close monitoring of the oral cavity allows for timely diagnosis and treatment of fungal, viral, and bacterial infections. Oral cultures and/or biopsies of all suspicious lesions are appropriate if medical status permits. While waiting for the results, empiric therapy typically is initiated until laboratory results dictate more specific medications.<sup>4,12,21</sup> Of note, nystatin is not effective for the prevention and/or treatment of fungal infections.<sup>11,42</sup>

Oral bleeding: Oral bleeding in patients undergoing immunosuppressive therapy commonly occurs due to thrombocytopenia and/or damaged vascular integrity. Management consists of local (e.g., pressure packs, antifibrinolytic rinses or topical agents, gelatin sponges) and systemic (e.g., platelet transfusions, aminocaproic acid) measures.<sup>11,12,21</sup>

Dental sensitivity/pain: Tooth sensitivity may be related to dry mouth during chemotherapy or head and neck radiation therapy and the lowered salivary pH.<sup>11,12,21</sup> Patients who are using plant alkaloid chemotherapeutic agents (e.g., vincristine, vinblastine) may experience neurotoxicity that presents as deep, constant jaw pain (affecting the mandibular molars with greater frequency) or paresthesia in the absence of odontogenic pathology. The pain usually is transient and generally subsides shortly after dose reduction and/or cessation of chemotherapy.<sup>11,12,21</sup>

Dry mouth: Sugar-free chewing gum or candy, sucking tablets, special dentifrices for oral dryness, saliva substitutes, frequent sipping of water, alcohol-free oral rinses, and/or oral moisturizers are recommended.<sup>5,12,43</sup> Placing a humidifier by the child's bedside at night may be useful.<sup>21</sup> Fluoride rinses and gels are highly recommended for caries prevention in these patients.

Trismus: Daily oral stretching exercises/physical therapy should be implemented during head and neck radiation treatment. Management of trismus may include prosthetic aids to reduce the severity of fibrosis, trigger-point injections, analgesics, muscle relaxants, and other pain management strategies.<sup>11,22,44</sup>

### Hematopoietic cell transplantation

Hematopoietic cell transplantation is used in children to treat malignancies and hematologic disorders, as well as certain metabolic syndromes. Examples include:<sup>45</sup>

- malignant disorders treated with autologous HCT
  - brain tumors.
  - Ewing sarcoma.
  - germ cell tumors.
  - Hodgkin lymphoma.
  - leukemia.
  - neuroblastoma.
  - non-Hodgkin lymphoma.
  - Wilms tumor.

- malignant disorders treated with allogenic HCT
  - acute lymphocytic leukemia.
  - acute myeloid leukemia.
  - high-risk solid tumors.
  - juvenile myelomonocytic leukemia.
  - myelodysplastic syndrome.
- nonmalignant disorders treated with allogenic HCT
  - bone marrow failure syndromes.
  - chronic granulomatous disease.
  - Fanconi anemia.
  - metabolic storage disorders.
  - osteopetrosis.
  - severe aplastic anemia.
  - sickle cell anemia.
  - thalassemia.
  - Wiskott-Aldrich syndrome.

Specific oral complications can be correlated with phases of HCT.<sup>3,4,7,10,15</sup>

#### *Phase I: Preconditioning*

The oral complications are related to the patient's current systemic and oral health, oral manifestations of the underlying condition, and oral complications of recent medical therapy. Oral complications observed include opportunistic infections, gingival leukemic infiltrates, bleeding, and ulceration.<sup>4</sup> Most of the principles of dental and oral care before the transplant are similar to those discussed for patients undergoing immunosuppressive cancer therapy.<sup>13</sup> The two major differences in HCT 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. Elective dentistry will need to be postponed until immunological recovery has occurred, at least 100 days following HCT. This may be longer if chronic GVHD or other complications (e.g., persistent immunodeficiency) are present.<sup>12</sup> Therefore, all dental treatment should be completed before the patient undergoes HCT.

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

In this phase, which encompasses the day the patient is admitted to the hospital to begin the transplant conditioning to 30 days post-HCT, the majority of oral complications are related to the conditioning regimen and supportive medical therapies.<sup>12</sup> 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) may be present.<sup>4</sup> Oral mucositis usually begins seven to 10 days after initiation of conditioning, and symptoms continue approximately two weeks after the end of conditioning.<sup>4</sup> Among allogeneic transplant patients, acute GVHD can occur, causing more severe inflammation and severe mucositis symptoms. Acute GVHD may begin as early as two to three weeks after the start of HCT and continue up to two months posttransplant.

The timing of this presentation may help distinguish acute GVHD from chemotherapy-induced OM.<sup>4</sup> The patient may be followed closely to monitor and manage the oral changes and to reinforce the importance of optimal oral care. Elective dental procedures are avoided in this phase due to the patient's severe immunosuppression. If emergency treatment is necessary, the dentist should consult and coordinate with the attending transplant team.

#### *Phase III: Engraftment to hematopoietic recovery*

The intensity and severity of acute complications observed in Phase II usually begin to decrease three to four weeks after transplantation. During this phase, acute GVHD can become a concern for allogeneic graft recipients. Dry mouth, hemorrhage, neurotoxicity, temporomandibular dysfunction, and granulomas/papillomas also are observed sometimes.<sup>4</sup> With regard to opportunistic infections, oral fungal infections and herpes simplex virus infection are most likely.<sup>4</sup> HCT patients are particularly sensitive to intraoral thermal stimuli between two and four months posttransplant.<sup>12</sup> The mechanism is not well understood, but the symptoms usually resolve spontaneously within a few months. Topical application of neutral fluoride or desensitizing toothpastes helps reduce the symptoms.<sup>12</sup> A dental/oral examination should be performed and invasive dental procedures, including dental cleanings and soft tissue curettage, should be done only if authorized by the HCT team because of the patient's continued immunosuppression.<sup>12</sup> 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-HCT, the oral complications are predominantly related to the chronic toxicity associated with the conditioning regimen, including dry mouth, craniofacial growth abnormalities, late viral infections, chronic oral GVHD, and oral squamous cell carcinoma.<sup>4,12</sup> Unless the patient is neutropenic or with severe chronic GVHD, mucosal bacterial infections are less frequently seen. Periodic dental examinations with radiographs can be performed, but invasive dental treatment is to be avoided in patients with persistent profound impairment of immune function.<sup>12</sup> 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 immunosuppressive therapy ends are three-fold:

- to maintain optimal oral health.
- to reinforce to the patient/parents the importance of optimal oral and dental care for life.
- to address any dental issues that may arise as a result of the long-term effects of immunosuppressive therapy or head and neck radiation.

#### *Dental care*

**Periodic evaluation:** The patient should be seen every six 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 should be followed closely for signs of malignant transformation of their oral mucosa (e.g., oral squamous cell carcinoma).<sup>4,10,46</sup>

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

**Orthodontic treatment:** Orthodontic care may start or resume after completion of all therapy and after at least a two-year disease-free survival when the risk of relapse is decreased and the patient is no longer using immunosuppressive drugs.<sup>7</sup> 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, (4) choose the simplest method for the treatment needs, and (5) do not treat the lower jaw.<sup>47</sup> However, specific guidelines for orthodontic management, including optimal force and pace, remain undefined. Patients and their families may be made aware of the potential for a higher risk of orthodontic relapse among cancer survivors.<sup>48</sup> Patients who were on intravenous anti-angiogenic 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.<sup>47,49</sup> Consultation with the patient's caregivers and physician regarding the risks (e.g., prolonged treatment time, MRONJ, treatment modifications)<sup>49</sup> and benefits (e.g., reduced root resorption, anchorage, less relapse)<sup>49</sup> of orthodontic care in this situation is recommended.

**Oral surgery and invasive periodontal therapy:** Patients at risk for MRONJ or osteoradionecrosis should be managed in coordination with the oncology team in the hospital setting.<sup>27,28,30</sup> Elective invasive procedures are best avoided in these patients.<sup>27,49</sup>

#### *Long-term concerns*

Craniofacial, skeletal, and dental developmental issues are some of the complications faced by survivors<sup>3,7,8,12</sup> and usually develop among children who were less than six years of age

at the time of their cancer therapy.<sup>7,12</sup> 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.<sup>5,7,8</sup> 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.<sup>44</sup> Relapse or secondary malignancies can develop at this stage.<sup>4,46</sup> Routine periodic examinations are necessary to provide comprehensive oral healthcare. 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. 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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