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Best Practices on Dental Management of Pediatric Patients Receiving ~~Chemotherapy, Hematopoietic Cell Transplantation~~, Immunosuppressive Therapy and/or Radiation Therapy

Review Council

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Keywords: Hematopoietic Stem Cell transplantation (HSCT), Low-level laser therapy (LLLT), Oral mucositis (OM), radiation therapy, chemotherapy, pediatric patient, immunosuppressed patient hematologic considerations.

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 which lowers the body's normal immune response. This can be deliberate as in lowering the immune response to prevent the rejection of an organ or hematopoietic stem cell transplant (**HSCT**) or it can be incidental as in a side effect of chemotherapy, radiation therapy, or HSCT conditioning. Dental intervention with certain modifications must be done promptly and efficiently, with attention to the patient's medical history, treatment protocol, and health status

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

Methods

~~This guideline was~~ Originally developed by the Clinical Affairs Committee as Dental Management of Pediatric Patients Receiving Chemotherapy, Hematopoietic Cell Transplantation and/or Radiation Therapy ~~and adopted~~ in 1986, this document was ~~is a revision of the previous version~~, last revised in 2013 ~~2008~~. This revision included a ~~new~~ systematic literature search of the PubMed® electronic database 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, and practice guideline; field: all; limits: within the last 10 years, humans, English, clinical trials, birth through age 18. ~~Sixty one thousand four hundred thirty two articles matched these criteria. One hundred thirty three 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 ~~oncologists~~ physicians, nurses, social workers, dieticians, dentists and other related health professionals is essential in caring for the child before, during and after any ~~cancer~~ immunosuppressive therapy[1,2]. ~~The oral cavity is highly susceptible to the effects of chemotherapy and radiation and is the most frequently documented source of sepsis in the immunosuppressed cancer patients. For these reasons, early and definitive dental intervention, including comprehensive oral hygiene measures, reduces the risk for oral and associated systemic complications (Hong, Brennan and Lockhart 2009, Scully and Epstein 1996, Hong et al 2010, Lalla Brennan and Schubert 2011, Elad et al 2008, Stiff et al 2006, Schubert and Peterson 2009, Bavier 1990, Little et al 2012, Semba, Mealy and Hallmon 1994, Sonis, Fazio and Fang 1995, Peterson, Bensadoun and Roila 2011/2012).~~

~~Acute oral sequelae as a result of cancer therapies and HCT regimens are common in children (Hong, Brennan and Lockhart 2009).~~ Oral and associated systemic complications that may occur as a sequelae of immunosuppressive therapy ~~may~~ include pain, mucositis, oral ulcerations, bleeding, taste dysfunction, secondary infections (e.g., candidiasis, herpes simplex virus), dental caries, salivary gland dysfunction (e.g., xerostomia), neurotoxicity, mucosal fibrosis, gingival hypertrophy post-radiation osteonecrosis, bisphosphonate related osteonecrosis, soft tissue necrosis, temporomandibular dysfunction (e.g., trismus), craniofacial and dental developmental anomalies, and oral graft versus host disease (**GVHD**)[1,3,4].

All patients ~~with cancer~~ undergoing immunosuppressive therapy should have an oral examination prior to the initiation of ~~the oncology therapy~~ treatment[1,2]. Prevention and treatment of pre-existing or concomitant oral disease is essential to minimize complications in this population[5]. The key to success in maintaining a healthy oral cavity during ~~cancer~~ therapy is patient compliance. The child and the parents should be educated regarding the possible acute side effects and the long-term sequelae of ~~cancer~~ immunosuppressive therapies in the oral cavity[3,5-9] (~~Scully and Epstein 1996~~, ~~da Fonseca 1998, da Fonseca 2000~~). ~~Because there are many oncology and HCT protocols,~~ Every patient should be managed on an individual basis; consultations with the patient's physicians and, when appropriate, other dental specialists should be sought before dental care is instituted[7].

Recommendations

Dental and oral care before the initiation of ~~cancer therapy~~ immunosuppressive therapy

Objectives

The objectives of a dental/oral examination before ~~cancer~~ therapy starts are three-fold to[9]: (~~da Fonseca 2000~~):

- ~~To~~ Identify and stabilize or eliminate existing and potential sources of infection and local irritants in the oral cavity—without needlessly delaying ~~the cancer~~ treatment or inducing complications.
- ~~To~~ Communicate with the medical ~~oncology~~ 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 in order to minimize oral problems/discomfort before, during, and after treatment and about the possible acute and long-term effects of the therapy in the oral cavity and the craniofacial complex.

Initial evaluation

Medical history review: should include, but not be limited to, disease/condition (type, stage, prognosis), treatment protocol (conditioning regimen, surgery, chemotherapy, radiation, transplant), medications (including bisphosphonates), allergies, surgeries, secondary medical diagnoses, hematological status [complete blood count (**CBC**)], coagulation status, immunosuppression status, presence of an indwelling venous access line, and contact of ~~oncology~~ medical team/primary care physician(s)[1]. For HSCT patients, include type of transplant, HSCT source (i.e., bone marrow, peripheral stem cells, cord blood stem cells), matching status, donor, conditioning protocol, expected date of transplant, and ~~presence of~~ GVHD prophylaxis ~~or signs of transplant rejection~~. ~~The American Heart Association (**AHA**) recommends that~~

~~antibiotic prophylaxis for nonvalvular devices, including indwelling vascular catheters (i.e., central lines) is indicated only at the time of placement of these devices in order to prevent surgical site infections (Baddour et al 2010, Hong et al 2010, Lockhart et al 2007). The AHA found no convincing evidence that microorganisms associated w ith dental procedures cause infection of nonvalvular devices at any time after implantation (Baddour et al 2010, Hong et al 2010, Lockhart et al 2007). The infections occurring after device implantation most often are caused by staphyloccal Gram-negative bacteria or other microorganisms associated with surgical implantation or other active infections (Baddour et al 2010, Hong et al 2010). Due to the risk of antibiotic adverse events, development of drug resistance among oral flora, spectrum of non-oral bacteria causing catheter-related infections, and lack of evidence from clinical trials, antibiotic prophylaxis is not necessary for patients with an indwelling central venous catheter who are undergoing dental procedures (Baddour et al 2010, Hong et al 2010). Immunosuppression is not an independent risk factor for nonvalvular device infections; immunocompromised hosts who have those devices should receive antibiotic prophylaxis as advocated for immunocompetent hosts (Baddour et al 2010, Hong et al 2010, Lockhart et al 2007, Wilson et al 2007). Consultation with the child's physician is recommended for management of patients with nonvalvular devices.~~ Patients with a compromised immune system may not be able to tolerate a transient bacteremia following invasive dental procedures. The decision regarding the need for antibiotic prophylaxis for dental procedures should be made in consultation with the child's physician. Unless advised otherwise by the physician, the American Heart Association's standard regimen to prevent endocarditis is an accepted option[2,10].

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

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

Preventive strategies

Oral hygiene: Oral hygiene includes brushing of the teeth and tongue two to three times daily with regular soft nylon brush or electric toothbrush, regardless of the hematological status[7,8,11,12] (~~Bavier 1990~~, ~~Ransier et al 1995~~). Ultrasonic brushes and dental floss should be allowed only if the patient is properly trained[8]. If capable, the patient's teeth should be gently flossed daily. If pain or excessive bleeding occurs, the patient should avoid the affected area, but floss the other teeth[1]. Patients with poor oral hygiene and/or periodontal disease may use chlorhexidine rinses daily until the tissue health improves or mucositis

develops[13]. The high alcohol content of commercially-available chlorhexidine mouthwash may cause discomfort and dehydrate the tissues in patients with mucositis; thus, an alcohol-free chlorhexidine solution is indicated in this situation.

For Immunosuppressed Patients

Oral hygiene: Intensive oral care is of paramount importance because it reduces the risk of developing moderate/severe mucositis without causing an increase in septicemia and infections in the oral cavity[1,3,5-8,11,14,15]. Thrombocytopenia should not be the sole determinant of oral hygiene as patients are able to brush without bleeding at widely different levels of platelet count[8]. Patients should use a soft nylon brush two to three times daily and replace it on a regular (every two to three months) basis[8,11]. Fluoridated toothpaste may be used but, if the patient does not tolerate it during periods of mucositis due to oral burning or stinging sensations, it may be discontinued and the patient should switch to mild-flavored non-fluoridated toothpaste. If moderate to severe mucositis develops and the patient cannot tolerate a regular soft nylon toothbrush or an end-tufted brush, foam brushes or super soft brushes soaked in chlorhexidine may be used[9]. Otherwise, foam or super soft brushes should be discouraged because they do not allow for effective cleaning[2]. The use of a regular brush should be resumed as soon as the mucositis improves[8,11,16]. Brushes should be air-dried between uses[8]. Electric or ultrasonic brushes are acceptable if the patient is capable of using them without causing trauma and irritation[8]. If patients are skilled at flossing without traumatizing the tissues, it is reasonable to continue flossing throughout treatment[8]. Toothpicks and water irrigation devices should not be used when the patient is pancytopenic to avoid tissue trauma[8,15].

Diet: Dental practitioners should ~~encourage~~ discuss the importance of a healthy diet to maintain nutritional status with an emphasis on foods that do not promote caries. ~~a non-cariogenic diet and advise~~ Patients and parents should be advised about the high cariogenic potential of dietary supplements rich in carbohydrates and oral pediatric medications rich in sucrose[6]. They should also be instructed that sharp, crunchy, spicy, highly acidic foods and alcohol should be avoided during chemotherapy, radiation and HCT[1].

Fluoride: Preventive measures include the use of fluoridated toothpaste ~~or gel~~, fluoride supplements if indicated, neutral fluoride gels/rinses, or applications of fluoride varnish for patients at risk for caries and/or xerostomia[6,8]. A brush-on technique is convenient and may increase the likelihood of patient compliance with topical fluoride therapy[8].

Lip care: Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products[8] (~~Semba, Mealy and Hallmon 1994~~).

Trismus prevention/treatment: Patients who receive radiation therapy to the masticatory muscles may develop trismus. Thus, daily oral stretching exercises/physical therapy should start before radiation is initiated and continue throughout treatment[7,15]. ~~Therapy for trismus may include prosthetic aids to reduce the severity of fibrosis, trigger-point injections, analgesics, muscle-relaxants, and other pain management strategies (Scully and Epstein 1996~~).

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

Education: Patient <u>and</u> parent education includes the importance of optimal oral care in order to minimize oral problems <u>and</u> discomfort before, during, and after treatment and the possible acute and long-term effects of the therapy in the craniofacial complex[1].

Dental care

Hematological considerations[4]:

- Absolute neutrophil count (**ANC**):
  - — >2,000/mm^3: no need for antibiotic prophylaxis[1,15];
  - — 1000 to 2000/mm^3: Use clinical judgment[1] based on the patient's health status and planned procedures. Some authors[1,7] suggest that antibiotic coverage (dosed per AHA recommendations[13]) may be prescribed when the ANC is between 1,000 and 2,000/mm^3. If infection is present or unclear, more aggressive antibiotic therapy may be indicated and should be discussed with the medical team; and
  - — <1,000/mm^3: defer elective dental care[4]. In dental emergency cases, discuss antibiotic coverage (antibiotic prophylaxis versus antibiotic coverage for a period of time) with medical team before proceeding with treatment. The patient may need hospitalization for dental management ~~(Sonis, Fazio and Fang 1995).~~
- Platelet count[4,7]:
  - — >75,000/mm^3: no additional support needed;

- 40,000 to 75,000/mm^3: platelet transfusions may be considered pre- and 24 hours post-operatively. Localized procedures to manage prolonged bleeding may include sutures, hemostatic agents, pressure packs, and/or gelatin foams; and
- <40,000/mm^3: defer care. In dental emergency cases, contact the patient's physician to discuss supportive measures (e.g., platelet transfusions, bleeding control, hospital admission and care) before proceeding. In addition, localized procedures (e.g., microfibrillar collagen, topical thrombin) and additional medications as recommended by the hematologist/oncologist (e.g., aminocaproic acid, tranexamic acid) may help control bleeding[1]).

- Other coagulation tests may be in order for individual patients.

Dental procedures:

- ~~In general terms, most oncology/hematology protocols (exclusive of HCT, which will be discussed later) are divided into phases (cycles) of chemotherapy, in addition to other therapies (e.g., radiotherapy, surgery). The patient's blood counts normally start falling five to seven days after the beginning of each cycle, staying low for approximately 14 to 21 days, before rising again to normal levels for a few days until the next cycle begins.~~ Ideally, all dental care should be completed before ~~cancer~~ 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[1,7], The patient's blood counts normally start falling five to seven days after the beginning of ~~each cycle,~~ treatment cycle staying low for approximately 14 to 21 days, before rising again to normal levels for a few days until the next cycle begins.
- Prioritizing procedures: When all dental needs cannot be treated before ~~cancer~~ therapy is initiated, priorities should be infections, extractions, periodontal care (e.g., scaling, prophylaxis), and sources of tissue irritation before the treatment of carious teeth, root canal therapy for permanent teeth, and replacement of faulty restorations[4,15]. The risk for pulpal infection and pain determine which carious lesions should be treated first[8]. Incipient to small carious lesions may be treated with fluoride, silver diamine fluoride and/or sealants until definitive care can be accomplished[7]. Some patients requiring an organ transplant will be best able to tolerate dental care at least three months after transplant when overall health improves[2]. It is important for the practitioner to be aware that the signs and symptoms of periodontal disease may be decreased in immunosuppressed patients[7].
- Pulp therapy in primary teeth: ~~Although there have been no studies to date that address the~~ Few studies have evaluated the safety of performing pulp therapy in primary teeth prior to the

initiation of chemotherapy and/or radiotherapy. Many clinicians choose to provide a more definitive treatment in the form of extraction because pulpal/periapical/furcal infections during immunosuppression periods can become life-threatening[4,7,8] (~~Semba, Mealy and Hallmon 1994~~). Teeth that already have been treated pulpally and are clinically and radiographically sound should be monitored periodically for signs of internal resorption or failure due to pulpal/periapical/furcal infections.

- Endodontic treatment in permanent teeth: Symptomatic non-vital permanent teeth should receive root canal treatment at least one week before initiation of ~~cancer~~ therapy to allow sufficient time to assess treatment success before the chemotherapy[4,7,15]. If that is not possible, extraction is indicated. Extraction is also the treatment of choice for teeth that cannot be treated by definitive endodontic treatment in a single visit. In that case, the extraction should be followed by antibiotic therapy (penicillin or, for penicillin-allergic patients, clindamycin) for about one week[7,15] (~~Sonis, Fazio and Fang 1995~~). Endodontic treatment of asymptomatic non-vital permanent teeth may be delayed until the hematological status of the patient is stable[4,15] (~~Semba, Mealy and Hallmon 1994~~, ~~Peters et al 1993~~). It is important that the etiology of periapical lesions associated with previously endodontically treated teeth be determined because they can be due to a number of factors including pulpal infections, inflammatory reactions, apical scars, cysts, and malignancy[8]. If a periapical lesion is associated with an endodontically treated tooth and no signs or symptoms of infection are present, there is no need for retreatment or extraction since the radiolucency likely is due to an apical scar[17] (~~Peters et al 1993~~).
- Orthodontic appliances and space maintainers: Poorly-fitting appliances can abrade oral mucosa and increase the risk of microbial invasion into deeper tissues[7]. Appliances should be removed if the patient has poor oral hygiene and/or the treatment protocol or HCT conditioning regimen carries a risk for the development of moderate to severe mucositis[4]. Simple appliances (e.g., band and loops, fixed lower lingual arches) that are not irritating to the soft tissues may be left in place in patients who present good oral hygiene[4,8]. Removable appliances and retainers that fit well may be worn as long as tolerated by the patient who maintains good oral care[7,8] (~~Sheller and Williams 1996~~). 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[7]. Consider removing orthodontic bands or adjusting prosthesis 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[8].

- Periodontal considerations: Partially erupted molars can become a source of infection because of pericoronitis. The overlying gingival tissue should be excised if the dentist believes it is a potential risk and if the hematological status permits[8,15]. Patients should have a periodontal assessment and appropriate therapy prior to receiving bisphosphonates as part of ~~cancer~~ treatment[18-20]. Extraction is the treatment of choice for teeth with a poor prognosis that cannot be treated by definitive periodontal therapy. If the patient has had bisphosphonates and an invasive periodontal procedure is indicated, risks must be discussed with the patient, parents, and physicians prior to the procedure.
- Extractions: There are no clear recommendations for the use of prophylactic antibiotics for extractions[4]. Recommendations generally have been empiric or based on anecdotal experience. Surgical procedures must be as atraumatic as possible, with no sharp bony edges remaining and satisfactory closure of the wounds[7,8,15,] (~~Semba, Mealy and Hallmon 1994, Sonis, Fazio and Fang 1995~~). If there is documented infection associated with the tooth, antibiotics (ideally chosen with the benefit of sensitivity testing) should be administered for about one week[7,8,15] (~~Sonis, Fazio and Fang 1995~~).

To minimize the risk of development of osteonecrosis, osteoradionecrosis, or bisphosphonate-related osteonecrosis of the jaw (**BRONJ**), patients who will receive radiation to the jaws or bisphosphonate treatment as part of the ~~cancer~~ therapy must have all oral surgical procedures completed before those measures are instituted[18-20]. If the patient has received bisphosphonates or radiation to the jaws and an oral surgical procedure is necessary, risks must be discussed with the patient, parents, and physician prior to the procedure. In patients undergoing long-term potent, high-dose intravenous bisphosphonates, there is an increased risk of BRONJ after a tooth extraction or with periodontal disease[18-20], although most of the evidence has been described in the adult population[19]. Patients with a high risk of BRONJ are best managed by a dental specialist in coordination with the ~~oncology~~ medical team in the hospital setting.

Loose primary teeth should be allowed to exfoliate naturally. Nonrestorable teeth, root tips, teeth with periodontal pockets greater than six millimeters, symptomatic impacted teeth, and teeth exhibiting acute infections, significant bone loss, involvement of the furcation, or mobility should be removed ideally two weeks (or at least seven to 10 days) before ~~cancer~~ therapy is initiated to allow adequate healing[4,7,8,15] (~~Semba, Mealy and Hallmon 1994~~).

Some practitioners prefer to extract all third molars that are not fully erupted, particularly prior to HCT, while others favor a more conservative approach, recommending extraction of third molars at risk for pulpal infection or those associated with significant pathology, infection, periodontal disease, or pericoronitis or if the tooth is malpositioned or non-functional[8,21,22].

Communication:

It is vital that the dentist communicate the comprehensive oral care plan with the ~~oncology~~ medical team. Information to be shared includes the severity of dental caries (number of teeth involved and which teeth need immediate treatment), endodontic needs (pulpal versus periapical infection), periodontal status, number of teeth requiring extraction, soft tissue pathology, and any other urgent care needed. Furthermore, it is important for the dentist to discuss with the ~~oncology~~ medical team how much time is needed for the stabilization of oral disease as this will also affect the timing of the treatment or conditioning protocols[1].

Dental and oral care during immunosupression periods

~~*Objectives*~~

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

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

~~*Preventive strategies*~~

~~Diet: Dental practitioners should encourage. a non-cariogenic diet and advise patients/parents about the high cariogenic potential of dietary supplements rich in carbohydrates and oral pediatric medications rich in sucrose (Hong et al 2010).~~

~~Fluoride: Preventive measures include the use of fluoridated toothpaste or gel, fluoride supplements if indicated, neutral fluoride gels/rinses, or applications of fluoride varnish for patients at risk for caries and/or xerostomia. A brush-on technique is convenient, familiar, and simple and may increase the likelihood of patient compliance with topical fluoride therapy (Schubert and Peterson 2009).~~

~~Lip care: Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products (Schubert and Peterson 2009, Semba, Mealy and Hallmon 1994).~~

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

Dental care

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

Management of oral conditions related to ~~cancer~~ immunosuppressive therapies

~~Trismus:~~

~~Trismus prevention/treatment: Patients who receive radiation therapy to the masticatory muscles may develop trismus. Thus, daily oral stretching exercises/physical therapy should start before radiation is initiated and continue throughout treatment. Therapy for trismus may include prosthetic aids to reduce the severity of fibrosis, trigger point injections, analgesics, muscle relaxants, and other pain management strategies (Scully and Epstein 1996, Lalla, Brennan and Schubert 2011, Little et al 2012).~~

~~Lip care: Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products (Schubert and Peterson 2009, Semba, Mealy and Hallmon 1994).~~

Mucositis:

~~Mucositis care remains focused on palliation of symptoms, and efforts to reduce the influence of secondary factors on mucositis, (Lalla, Brennan and Schubert 2011, Little et al 2012, Sonis, Fazio and Fang 1995, Keefe et al 2007).~~ The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published guidelines for treatment of mucositis[11,16,23]. The

most common prescriptions for management of mucositis include good oral hygiene, analgesics, non-medicated oral rinses (e.g., 0.9 percent saline or sodium bicarbonate mouth rinses four to six times/day), and parenteral nutrition as needed[1,11,14]. Mucosal coating agents (e.g., Amphojel®, Kaopectate®, hydroxypropylmethylcellulose) and film-forming agents (e.g., Zilactin®) and Gelclair® also have been suggested[1]. ~~The use of palifermin, also known as keratnocyte growth factor-1, for prevention of oral mucositis associated with HCT and oral cryotherapy as prophylaxis and treatment to decrease mucositis recently have been recommended (NCI 2016, Lalla et al 2014, Peterson, Bensadoun and Roila 2011/2012, Keefe et al 2007). Palifermin has been observed to decrease the incidence and duration of severe oral~~ *mucositis* ~~in patients undergoing conditioning with high-dose chemotherapy, with or without radiotherapy, followed by HCT (Lalla et al, 2014, Stiff et al 2006). The guidelines, however, did not recommend the use of sucralfate, antimicrobial lozenges, pentoxifylline, and granulocyte–macrophage-colony stimulating factor mouthwash for oral mucositis (Lalla et al 2014, Peterson, Bensadoun and Roila 2011/2012, Keefe et al 2007).~~

Effective interventions for mucositis prevention include the use of palifermin, low-level laser therapy (LLLT), and cryotherapy. The use of sucralfate, antimicrobial lozenges, pentoxifylline, and granulocyte–macrophage-colony stimulating factor mouthwash for oral mucositis are not recommended[11,16,23].

Palifermin (keratinocyte growth factor-1) is an FDA approved drug for the prevention and treatment of oral mucositis. Palifermin is recommended for mucositis prophylaxis for patients undergoing conditioning with high-dose chemotherapy and total body irradiation followed by HCT[23]. Palifermin is believed to stimulate epithelial cell reproduction, growth, and development so that mucosal cells damaged by chemotherapy and radiation are replaced quickly, accelerating the healing process[24].

~~There is limited, but encouraging, evidence to support the use of low-level laser therapy to decrease the duration of chemotherapy-induced oral mucositis; further studies are required to evaluate the efficacy and develop specific recommendations (Keefe et al 2007, Kuhn et al 2009, Migliorati et al 2013~~

The current MASCC/ISOO guidelines support the use of low-level laser therapy to prevent oral mucositis for patients undergoing HSC conditioning with high-dose chemotherapy with or without total body irradiation as well as patients undergoing radiation treatment for head and neck cancer[23]. Low-level laser therapy can decrease pain, duration and severity of chemotherapy induced mucositis in children[25-27]. LLLT 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 LLLT to prevent contamination and occupational risks to the child and dental team.

Oral cryotherapy, the cooling of intraoral tissue with ice during chemotherapy treatment, is recommended as mucositis prophylaxis for patients receiving bolus infusion of chemotherapy drugs with short half-lives[23,28]. This includes patients treated with fluorouracil as well as patients receiving high-dose melphalan as conditioning for HCT[23]. Oral cryotherapy reduces blood flow to the mouth by narrowing the blood vessels, 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 pediatric oncology[28].

Studies on the use of chlorhexidine for mucositis have given conflicting results. Most studies have not demonstrated a prophylactic impact or a reduction in the severity of mucositis, although reduced colonization of candidial species has been shown[14,16,29,30] (~~Sonis, Fazio and Fang 1995~~). Chlorhexidine is no longer recommended for preventing oral mucositis in patients undergoing radiotherapy[11,23].

Patient-controlled analgesia has been helpful in relieving pain associated with mucositis, reducing the requirement for oral analgesics. There is no significant evidence of the effectiveness or tolerability of mixtures containing topical anesthetics (e.g., Philadelphia mouthwash, magic mouthwash)[16] The use of topical anesthetics has been recommended for pain management although there are no studies available to assess the benefit and potential for toxicity. Topical anesthetics only provide short term pain relief[11]. Lidocaine use may obtund or diminish taste and the gag reflex and/or result in a burning sensation, in addition to possible cardiovascular and central nervous system effects.

Oral mucosal infections: The signs of inflammation and infection may be greatly diminished during neutropenic periods. Thus, the clinical appearance of infections may differ significantly from the normal[15]. Close monitoring of the oral cavity allows for timely diagnosis and treatment of fungal, viral, and bacterial infections. Prophylactic nystatin is not effective for the prevention and/or treatment of fungal infections[7,31]. Oral cultures and/or biopsies of all suspicious lesions should be performed and prophylactic medications should be initiated until more specific therapy can be prescribed[1,7,8,15,] (~~Bavier 1990, Semba,~~ ~~Mealy and Hallmon 1994, Sonis, Fazio and Fang 1995~~).

Oral bleeding: Oral bleeding occurs due to thrombocytopenia, disturbance of coagulation factors, and/or damaged vascular integrity. Management should consist of local approaches (e.g., pressure packs, antifibrinolytic rinses or topical agents, gelatin sponges) and systemic measures (e.g., platelet transfusions, aminocaproic acid)[7,8,15].

Dental sensitivity/pain: Tooth sensitivity could be related to decreased secretion of saliva during radiation therapy and the lowered salivary pH[7,8,15]. Patients who are using plant alkaloid chemotherapeutic agents (e.g., vincristine, vinblastine) may present with deep, constant pain affecting the mandibular molars with greater frequency, in the absence of odontogenic pathology. The pain usually is transient and generally subsides shortly after dose reduction and/or cessation of chemotherapy[7,8,15].

Xerostomia: Sugar-free chewing gum or candy, sucking tablets, special dentifrices for oral dryness, saliva substitutes, frequent sipping of water, alcohol-free oral rinses, and/or oral moisturizers are recommended[8,32]. Placing a humidifier by bedside at night may be useful[15]. Saliva stimulating drugs are not approved for use in children. Fluoride rinses and gels are recommended highly for caries prevention in these patients.

Trismus: Daily oral stretching exercises/physical therapy must continue during radiation treatment. Management of trismus may include prosthetic aids to reduce the severity of fibrosis, trigger-point injections, analgesics, muscle relaxants, and other pain management strategies[7,15] ~~(Scully and Epstein 1996)~~.

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

~~*Objectives*~~

~~The objectives of a dental/oral examination after cancer therapy ends are 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 and/or treat any dental issues that may arise as a result of the long-term effects of cancer therapy.~~

~~*Preventive strategies*~~

~~Oral hygiene: Patients must brush their teeth two to three times daily with a soft nylon toothbrush. Brushes should be air-dried between uses (Schubert and Peterson 2009). Patients should floss daily.~~

~~Diet: Dental practitioners should encourage a non-cariogenic diet and advise patients/parents about the high cariogenic potential of dietary supplements rich in carbohydrates and oral pediatric medications rich in sucrose (Hong et al 2010~~

~~Fluoride: Preventive measures include the use of fluoridated toothpaste and gel, fluoride supplements if indicated, neutral fluoride gels/rinses, or applications of fluoride varnish for patients at risk for caries and/or xerostomia. A brush-on technique is convenient, familiar, and simple and may increase the likelihood of patient compliance with topical fluoride therapy (Schubert and Peterson 2009).~~

~~Lip care: Lanolin-based creams and ointments are more effective in moisturizing and protecting against damage than petrolatum-based products (Schubert and Peterson 2009, Semba, Mealy and Hallmon 1994).~~

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

~~*Dental care*~~

~~Periodic evaluation: The patient should be seen at least every six months (or in shorter intervals if issues such as chronic oral GVHD, xerostomia, or trismus are present). Patients who have experienced moderate or severe mucositis and/or chronic oral GVHD should be followed closely for malignant transformation of their oral mucosa (e.g., oral squamous cell carcinoma) (Elad et al 2008, Euvrard et al 2003).~~

~~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 (Sheller and Williams 1996). A thorough assessment of any dental developmental disturbances caused by the cancer therapy must be performed before initiating orthodontic treatment. The following strategies should be considered when providing orthodontic care for patients with dental sequelae: (1) use appliances that minimize the risk of root resorption, (2) use lighter forces, (3) terminate treatment earlier than normal, (4) choose the simplest method for the treatment needs, and (5) do not treat the lower jaw (Zahrowski 2007). However, specific guidelines for orthodontic management, including optimal force and pace, remain undefined. Patients who have used or will be~~

~~given bisphosphonates in the future present a challenge for orthodontic care. Although bisphosphonate inhibition of tooth movement has been reported in animals, it has not been quantified for any dose or duration of therapy in humans (Zahrowski 2007). Consultation with the patient's parents and physician regarding the risks and benefits of orthodontic care in this situation is recommended.~~

~~Oral surgery: Consultation with an oral surgeon and/or periodontist and the patient's physician is recommended for non-elective oral surgical and invasive periodontal procedures in patients who have used or are using bisphosphonates or those who received radiation therapy to the jaws in order to devise strategies to decrease the risk of osteonecrosis and osteoradionecrosis, respectively (Saad et al 2012, Kuhl et al 2012, Dodson 2009). Elective invasive procedures should be avoided in these patients (Dahllöf et al 2001). Patients with a high risk of BRONJ are best managed by in coordination with the oncology team in the hospital setting.~~

~~Xerostomia: Sugar-free chewing gum or candy, special dentifrices for oral dryness, saliva substitutes, frequent sipping of water, alcohol-free oral rinses, and/or oral moisturizers are recommended (Schubert and Peterson 2009, Euvrard, Kanitakis and Claudy 2003, Jensen et al 2010). Placing a humidifier by bedside at night may be useful (Little et al 2012). Saliva stimulating drugs are not approved for use in children. Fluoride rinses and gels are recommended highly for caries prevention in these patients.~~

~~Trismus: Daily oral stretching exercises/physical therapy should continue after radiation therapy is finished in order to prevent or ameliorate trismus. Management of trismus may include prosthetic aids to reduce the severity of fibrosis, trigger point injections, analgesics, muscle relaxants, and other pain management strategies (Scully and Epstein 1996, Lalla, Brennan and Schubert 2011, Little et al 2012).~~

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplant can be used in children to treat malignancies, hematologic disorders as well and certain metabolic syndromes. Examples include:

Malignant disorders treated with autologous HSCT

leukemia

Brain tumors

Ewing sarcoma

Germ cell tumors

Hodgkin lymphoma
Neuroblastoma
Non-Hodgkin lymphoma
Retinoblastoma
Rhabdomyosarcoma
Wilms tumor

Malignant disorders treated with allogenic HSCT
Acute lymphocytic leukemia
Acute myeloid leukemia
Juvenile myelomonocytic leukemia
Myelodysplastic syndrome
High-risk solid tumors

Non-malignant disorders treated with allogenic HSCT
Bone marrow failure syndromes
Chronic granulomatous disease
Fanconi anemia
Metabolic storage disorders
Osteogenesis imperfecta
Osteopetrosis
Severe aplastic anemia
Sickle cell anemia
Thalessemia
Wiskott-Aldrich syndrome

Specific oral complications can be correlated with phases of HSCT[1,4,8] (~~da Fonseca 1998~~).

Phase I: Preconditioning

The oral complications are related to the current systemic and oral health, oral manifestations of the underlying condition, and oral complications of recent medical therapy. Oral complications observed include oral infections, gingival leukemic infiltrates, bleeding, ulceration, temporomandibular

dysfunction[1]. Most of the principles of dental and oral care before the transplant are similar to those discussed for pediatric cancer[9]. The two major differences are: 1) in HSCT, the patient receives all the chemotherapy and/or total body irradiation in just a few days before the transplant, and 2) there will be prolonged immunosuppression following the transplant. Elective dentistry will need to be postponed until immunological recovery has occurred, at least 100 days following HSCT, or longer if chronic GVHD or other complications are present[7,8]. Therefore, all dental treatment should be completed before the patient becomes immunosuppressed.

Phase II: Conditioning neutropenic phase

In this phase, which encompasses the day the patient is admitted to the hospital to begin the transplant conditioning to 30 days post-HCT, the oral complications are related to the conditioning regimen and supportive medical therapies[8]. Mucositis, xerostomia, oral pain, hemorrhage, opportunistic infections, taste dysfunction, neurotoxicity (including dental pain, muscle tremors), and temporomandibular dysfunction (including jaw pain, headache, joint pain) may be seen, typically with a high prevalence and severity of oral complications[1]. Oral mucositis usually begins seven to 10 days after initiation of conditioning, and symptoms continue approximately two weeks after the end of conditioning[1]. Among allogeneic transplant patients, hyperacute GVHD can occur, causing more severe inflammation and severe mucositis symptoms, although its clinical presentation is difficult to diagnose[1]. The patient should be followed closely to monitor and manage the oral changes and to reinforce the importance of optimal oral care. Dental procedures usually are not allowed in this phase due to the patient's severe immunosuppression. If emergency treatment is necessary, the dentist should consult and coordinate with the attending ~~hematology/oncology~~ transplant team.

Phase III: Engraftment to hematopoietic recovery

The intensity and severity of complications begin to decrease normally three to four weeks after transplantation. Oral fungal infections and herpes simplex virus infection are most notable[1]. Acute GVHD can become a concern for allogeneic graft recipients. Xerostomia, hemorrhage, neurotoxicity, temporomandibular dysfunction, and granulomas/papillomas sometimes are observed[1]. 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[8]. Patients should be encouraged to optimize oral hygiene and avoid a cariogenic diet. Attention to xerostomia and oral GVHD manifestations is crucial. HSCT patients are particularly sensitive to intraoral thermal stimuli between two and four months post-transplant[8]. 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[8].

Phase IV: Immune reconstitution/recovery from systemic toxicity

After day 100 post-HCT, the oral complications predominantly are related to the chronic toxicity associated with the conditioning regimen, including salivary dysfunction, craniofacial growth abnormalities, late viral infections, oral chronic GVHD, and oral squamous cell carcinoma[1,8]. Xerostomia and relapse-related oral lesions may also be observed[1]. 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 should be avoided in patients with profound impairment of immune function[8]. Consultation with the patient's physician and parents regarding the risks and benefits of orthodontic care is recommended.

~~*Phase V: Long-term survival*~~

~~Craniofacial, skeletal, and dental developmental issues are some of the complications faced by cancer survivors (NCI 2016, Schubert and Peterson 2009, da Fonseca 2011) and usually develop among children who were less than six years of age at the time of their cancer therapy (Schubert and Peterson 2009, da Fonseca 2011). Long term effects of cancer 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, and reduced alveolar process height (da Fonseca 2011). 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 xerostomia (Dahllöf et al 2001, Jensen et al 2010). Relapse or secondary malignancies can develop at this stage (NCI 2016). 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 when relapse or the patient's immunologic status declines.~~

Dental and oral care after ~~the cancer therapy~~ <u>immunosuppressive therapy</u> is completed ~~(exclusive of HCT)~~

Objectives

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

- ~~To~~ Mmaintain optimal oral health.
- ~~To~~ Rreinforce to the patient/parents the importance of optimal oral and dental care for life.
- ~~To~~ Aaddress and/or treat any dental issues that may arise as a result of the long-term effects of cancer therapy.

Dental care

Periodic evaluation: The patient should be seen at least every six months (or in shorter intervals if issues such as chronic oral GVHD, xerostomia, or trismus are present). Patients who have experienced moderate or severe mucositis and/or chronic oral GVHD should be followed closely for malignant transformation of their oral mucosa (e.g., oral squamous cell carcinoma)[5,33].

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

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[4] (~~Sheller and Williams 1996~~). A thorough assessment of any dental developmental disturbances caused by the ~~cancer~~ therapy must be performed before initiating orthodontic treatment. The following strategies should be considered when providing orthodontic care for patients with dental sequelae: (1) use appliances that minimize the risk of root resorption, (2) use lighter forces, (3) terminate treatment earlier than normal, (4) choose the simplest method for the treatment needs, and (5) do not treat the lower jaw[34]. However, specific guidelines for orthodontic management, including optimal force and pace, remain undefined. Patients who have used or will be given bisphosphonates in the future present a challenge for orthodontic care. Although bisphosphonate inhibition of tooth movement has been reported in animals, it has not been quantified for any dose or duration of therapy in humans[34]. Consultation with the patient's parents and physician regarding the risks and benefits of orthodontic care in this situation is recommended.

Oral surgery: Consultation with an oral surgeon and/or periodontist and the patient's physician is recommended for non-elective oral surgical and invasive periodontal procedures in patients who have used or are using bisphosphonates or those who received radiation therapy to the jaws in order to devise strategies to decrease the risk of osteonecrosis and osteoradionecrosis, respectively[18-20]. Elective invasive procedures should be avoided in these patients (~~Dahllöf et al 2001~~). Patients with a high risk of BRONJ are best managed by in coordination with the oncology team in the hospital setting.

Long Term Concerns

Craniofacial, skeletal, and dental developmental issues are some of the complications faced by ~~cancer~~ survivors[1,4,8] and usually develop among children who were less than six years of age at the time of their ~~cancer~~ therapy[4,8]. Long term effects of ~~cancer therapy~~ 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, and reduced alveolar process height[4]. 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 xerostomia[35] (~~Dahllöf et al 2001~~). Relapse or secondary malignancies can develop at this stage[1]. 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 ~~when~~ if relapse or the patient's immunologic status declines.

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