Oral Care for Hematopoietic Stem Cell Transplantation Patients: A Narrative Review

Firoozeh Samim[a] / Kim L. ten Böhmer[b] / Renée G.A. Koppelmans[c] / Judith E. Raber-Durlacher[d] / Joel B. Epstein[e]

Purpose: Patients undergoing hematopoietic stem cell transplantation (HSCT) are at high risk of oral complications with the potential of causing significant morbidity and mortality. Dental professionals should play a fundamental role in the prevention and treatment of oral sequelae of HSCT. However, the dental community is not well informed and experienced in providing oral care of the oral complications for HSCT patients. This narrative review attempts to fill the knowledge gap through reviewing the oral complications and current recommendations for oral and dental care for the patient before, during and after HSCT.

Results: Oral care in the HSCT process was divided into five stages with the goal being to provide practical guidance for dental care providers to assist in managing these patients. It is well known that the maintenance of good oral health is important in cancer patients, including patients with hematologic malignancies. In addition to negatively impacting quality of life, oral pain and/or infections can cause delays, modification and discontinuation of life-saving cancer treatment. Oral complications can lead to new or extended hospitalization. By providing a preventive and treatment algorithm based on currently available literature reports and expert opinion, we can hope to achieve better patient outcomes.

Conclusion: We present oral and dental management recommendations with a focus on oral health maintenance, infection prevention, pain control and oral complication management to support oral and general health of this medically complex patient population prior to, during and following HSCT.

Key words: hematopoietic stem cell transplantation, infection prevention, oral care, oral complication, pain control

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More than 50,000 hematopoietic stem cell transplants (HSCTs) are performed each year worldwide, and the number continues to grow by 10%-20% annually.[17] HSCT is utilized for treatment of hematopoietic malignancies and to allow chemotherapy intensification for selected diseases. HSCT provides an intravenous infusion of autologous (stem cells from the patient) or allogeneic stem cells (stem cells from a donor) collected from bone marrow, peripheral blood, or umbilical cord blood to re-establish hematopoietic function for the treatment of different malignant and non-malignant hematologic disorders, as well as some autoimmune diseases. The overall outcomes and survival rates post-HSCT have improved in the last two decades due to better overall patient selection, improvement in HLA-matching for donor selection, and advances in oncology care and improvement in supportive care. Among the HSCT patients who survived at least two years after autologous HSCT, 68.8% were alive ten years after transplantation.[5] As more patients survive longer, increased dental and oral care needs are anticipated. In addition, HSCT is now available for older patients who may have more dental pathologies. However, the current dental community has not been well prepared for the management of these unique patients prior to, during and following HSCT.[11] A recent survey shows that while most dentists are aware of the importance

[a] *Clinical Assistant Professor, McGill Dental School and Director of Oral Medicine/ Oral Pathology, Janeway Hospital, Eastern health/Memorial University (MUN), St John's, NL, Canada. All authors contributed equally to this work.*

[b] *Dentist, Department of Oral Medicine, Academic Centre for Dentistry Amsterdam, University of Amsterdam and Vrije Universiteit Amsterdam, Amsterdam, the Netherlands.*

[c] *Dentist, Department of Oral and Maxillofacial Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands.*

[d] *Associate Professor, Amsterdam University Medical Center (UMC), University of Amsterdam, Department of Oral and Maxillofacial Surgery, Amsterdam, the Netherlands; Academic Centre for Dentistry Amsterdam (ACTA), Department of Oral Medicine, Amsterdam, the Netherlands.*

[e] *Professor, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; Director, Dental Oncology Service, Division of Otolaryngology and Head and Neck Surgery, City of Hope, Duarte, CA, USA.*

Correspondence: *Dr. Joel B. Epstein, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, 90048, USA.*
e-mail: joel.epstein@cshs.org

of dental care during HSCT, they are not familiar with the oral care needs of these patients and the considerations of dental treatment planning.[7] The purpose of this article is to summarize oral complications and provide recommendations for oral and dental care before, during and after HSCT.

Candidates for HSCT are prepared for transplant using different preoperative regimens described as conditioning therapy, which may include chemotherapy, targeted therapies and immunotherapies with or without total body irradiation (TBI) or total lymphoid irradiation (TLI). This may begin 3–10 days before the transplant.[2,5,17] For prevention of graft-versus-host disease (GVHD) in allogeneic HSCT, recipients may be given immunosuppressive agents such as prednisone, cyclosporine, and methotrexate. In addition to the underlying medical disease, conditioning therapies and the immunosuppressive regimen may result in oral toxicities. The presence of any sources of oral infections or trauma may put the patient at higher risk for complications which may result in new or extended hospitalization and costs, and lower quality of life.[7,11,20,33] Adapting a multidisciplinary approach by establishing a collaborative medical, dental, nursing, nutrition, physical therapy and counselling, providers in each transplant center and in the community may facilitate the delivery of optimal care for HSCT patients.[11]

SHORT- AND LONG-TERM ORAL COMPLICATIONS AFTER HSCT

The oral cavity is highly susceptible to the effects of the conditioning regimen with or without total body radiation (TBI), and is the most frequently documented source of infection in the immunosuppressed cancer patients.[46] Oral complications are common and reported in 80% of patients.[15] Acute oral complications of HSCT regimens include pain, mucositis, oral ulcerations, oral bleeding, taste dysfunction, infections (e.g. candidiasis and herpes virus infection, pericoronitis, exacerbation of periodontal and periapical infections), and acute oral graft versus host disease (GVHD). Chronic complications include pain, salivary gland dysfunction, dental sensitivity and dental caries, oral mucosal infection (e.g. candidiasis, herpes virus infection), neurotoxicity, taste change, soft tissue fibrosis, osteonecrosis, temporomandibular dysfunction (e.g. trismus), chronic oral GVHD and secondary malignancy (e.g. oral squamous cell carcinoma [SSC]).[13]

PHASES OF ORAL CARE IN HSCT PATIENTS

Immunosuppressed HSCT patients require regular and special oral care, which should be considered individually according to the status of their underlying disease(s), medical condition, and prior transplant therapies and oral conditions. The complexities of HSCT protocols also require each patient to be managed individually. Dental intervention with certain modifications must be completed promptly and coordinated with the patients' oncology team and, when necessary, with dentists who have expertise in oncology care. [29]

Oral/dental care of HSCT patients can be divided into five phases: prior to, during transplant admission, shortly after (up to 100 days) post-transplant, early long-term (up to 1-year post-transplant), and late long-term phases.[12,19,23,43] The post-transplant period consists of three phases: the pancytopenia phase, immune recovery phase, and long-term immunocompetent phase. We describe each phase to provide corresponding recommendations for oral and dental management (Table 1).

A: Phase I: Preconditioning (Prior to HSCT)

Phase I, the period before HSCT, is of variable duration based on the medical diagnosis, urgency of transplant and availability of donor and resources (Table 1). The goals of pre-treatment assessment are to identify and manage existing conditions that represent potential risks of oral diseases and infection, which may arise during neutropenia and in the first-year post-transplant. The patient should receive information about potential oral side effects of HSCT. A plan should be developed for establishing and maintaining oral hygiene, providing preventive care, and alleviating possible oral symptoms and complications during and after HSCT.

A.1 Oral examination and treatment planning

Ideally, a comprehensive oral evaluation and treatment plan should be completed within a month prior to HSCT to allow 1–2 weeks for healing if invasive dental procedures are required.[36] The pre-treatment evaluation includes a comprehensive examination of hard and soft tissues, including full periodontal evaluation, and appropriate radiographs to detect possible sources of infection and pathological conditions.[14]

In this phase, decisions about dental treatment (radical or conservative) depend on the dental and medical status of the patient, including cancer diagnosis, cancer treatment modalities, prior oral hygiene effectiveness, and time available prior to starting therapy.[11] The treatment plan should include: 1) professional dental cleaning (dental plaque and calculus removal), prophylaxis, and fluoride treatment in caries susceptible individuals;[26] 2) elimination of sources of infection; 3) elimination of sources of mucosal trauma/irritation (potentially traumatic edges of teeth, restorations or prostheses); and 4) direction in preventive dental care.

A.2: Patient education

Patient education is an integral part of the pre-transplant evaluation and should address possible oral complications of HSCT, maintaining adequate nutrition, avoidance of tobacco and alcohol, and the risk of secondary malignancy.[46] Patients should understand that good oral care during HSCT is thought to contribute to oral health, quality of life and decrease potential complications.[45] Oral hygiene includes brushing the teeth and dorsum of the tongue two to three times daily with a soft or ultra-soft toothbrush, and daily interdental cleaning regardless of the hematological status.[41] Guidelines for interdental cleaning depend on the skill of the patient and the ability to complete oral hygiene without trauma to tissue. Interdental cleaning can continue during thrombocytopenia if prolonged bleeding does not occur

Table 1 Five phases in HSCT patients and common oral complications in these phases

Phase I Preconditioning stage	Phase II Conditioning neutropenic stage	Phase III Engraftment stage (first 100 days)	Phase IV Long-term stage 1 (day +100 – 180)	Phase V Long-term stage 2 (> day 180)
Dental hygiene including oral rinse, fluoride, recommended through all phases Symptoms such as pain and salivary change seen in all phases Oral/dental conditions causing mucosal trauma or local/systemic infection up to Phase V				
Dental caries Pulpal pathology Gingivitis Periodontitis Pericoronitis Periimplantitis	Mucositis Dental emergencies	Acute GVHD* Infections Dental emergencies	Chronic GVHD* Infections Dental emergencies	Chronic GVHD* Gingival hyperplasia Infections Dental emergencies
Viral, bacterial or fungal infections	Viral, bacterial or fungal infections	Viral, bacterial or fungal infections	Viral, bacterial or fungal infections	Viral, bacterial or fungal infections
Gingival leukemic infiltrates			Post-transplant lympho-proliferative disorders Relapse-related oral lesions Granulomas/HP**	Post-transplant lympho-proliferative disorders Relapse-related oral lesions Granulomas/HP**
Xerostomia / hyposalivation	Xerostomia / hyposalivation	Xerostomia / hyposalivation	Xerostomia / hyposalivation	Xerostomia / hyposalivation Kaposi's sarcoma[1] Squamous cell carcinoma
Oral bleeding Thrombocytopenia[2]	Oral bleeding Thrombocytopenia[2]	Oral bleeding	Secondary malignancy	Secondary malignancy
Oral ulceration	Neurotoxicity Neutropenia[2]	Neurotoxicity	Neurotoxicity	Neurotoxicity
Temporomandibular disorder (TMD)	TMD+	TMD+	TMD+	TMD+ Loss of bone density

*Graft-versus-host disease; ** human papilloma virus+ temporomandibular disorder; [1] Buzea CM, Cuculescu M, Podoleanu E, Preoteasa CT, Ranga R. Dental treatment considerations for the organ and bone marrow transplant patient. Heart. 2009;5:2. http://www.wseas.us/e-library/transactions/biology/2009/89-169.pdf. Accessed September 1, 2016; [2] Nappalli D, Lingappa A. Oral manifestations in transplant patients. Dent Res J (Isfahan) 2015;12:199–208. https://www.ncbi.nlm.nih.gov/pubmed/?term=26005458. Accessed September 1, 2016

after oral care procedures. Patients with poor oral hygiene may by prescribed alcohol-free chlorhexidine rinses for daily use;[23] and can apply this with toothbrushes or foam brushes to improve plaque control.

A.3 Management of dental caries and periodontal diseases

The priorities in this phase are directed at sites of infection, periodontal care (e.g. scaling, prophylaxis) and sources of tissue irritation. In general, the risk for any hard or soft tissue infections and pain will determine the need for treatment prior to HSCT. Incipient caries may be treated with fluoride, remineralizing products and/or temporary restorations or sealants. Dental caries or defective restorations with a risk of pulpal infection should be stabilized.

It is important to be aware that the signs and symptoms of periodontal diseases may be decreased in patients with hematologic malignancy and previous myelosuppressive treatment.[29] Periodontal evaluation and management is of importance as periodontal disease may predispose for systemic infectious complications.[12,42] Anecdotal evidence suggests that meticulous oral hygiene measures and good periodontal health care are important for controlling oral GVHD.[32] Initial periodontal treatment aimed at reducing the oral microbial load and inflammation as well as oral hygiene instruction are important. Extraction of severely periodontally affected ('hopeless') teeth is indicated, but no recommendations can be given about specific pocket depths that necessitate extraction. Whereas some authors suggest that extraction of teeth with pockets depths > 4 mm is indicated, others recommend an extraction for teeth with ≥ 6 mm of pockets.[35] A large ongoing prospective multicenter study aims to provide more information about the role of periodontitis in the risk of developing complications in patients treated with different types of HSCT.[8]

A.4 Antibiotic prophylaxis

Antibiotic prophylaxis is considered in this phase if an infection is present when decreased neutrophil count or function is anticipated. The American Heart Association (AHA) found no convincing evidence that dental procedure-related microorganisms that result in a non-valvular device associated infection any time after implantation.[3,22,31] Due to the risk of antibiotic-related adverse effects including possible drug resistance of the oral flora, and catheter-related infections from non-oral bacteria, antibiotic prophylaxis is not recommended for patients with an indwelling central venous catheter and ongoing dental procedures. Consultation with the HSCT team with respect to antibiotic prophylaxis is appropriate.

A.5 Hematologic status and related treatment

The patient's hematologic status is critical information to understand prior to dental care. General hematologic considerations in pre-transplant dental care include the following.

Absolute neutrophil count (ANC): there is a lack of evidence-based literature regarding antimicrobial prophylaxis for neutropenic patients. Current recommendations support antibiotic prophylaxis if the ANC is less than 1000 for more than 7 days. The suggestion includes:[4,23,50] >1000/µl[5]: no need for antibiotic prophylaxis[18]; 1000–500/µl: consultation with the medical team is recommended;[19,18] <500/µl[5]: defer elective dental care if not emergent. Consider antibiotic prophylaxis based on AHA guidelines. In cases of dental emergency, consultation with oncology team is recommended.[3,18] Platelet count:[13,29] >50,00 µl.[5]: no additional support needed; <50,00 µl[5]: avoid invasive procedures; platelet transfusions may be considered pre- and 24 h post-operatively if the platelet count is less than 40,00 µl. Local procedures to manage bleeding may include sutures, hemostatic agents, pressure packs, and or gelatin foams. In dental emergency cases, contact the oncology team to discuss supportive measures (e.g. platelet transfusions, bleeding control, hospital admission and care) before proceeding. Also, local procedures (e.g. microfibrillar collagen, topical thrombin) and additional medications as recommended by the oncologist / dental specialist (e.g. aminocaproic acid, tranexamic acid) may help control bleeding.[15]

Other coagulation tests such as coagulation studies, liver function tests may be considered.

A.6 Surgery/extraction

Extraction of hopeless teeth and retained radices prior to HSCT is an important treatment strategy to eliminate a source of infection, prevent flare up of chronic disease during therapy, and reduce the need for post-HSCT extraction as well as development of medication-related osteonecrosis of the jaw (MRONJ). The risk of MRONJ is increased with the use of antiresorptive medication (e.g. bisphosphonates, denosumab) and anti-vascular drugs (e.g. bevacizumab) that might be prescribed to some of the patients. Any surgical intervention should be planned in consultation with the transplant team at least 7–10 days prior to conditioning (Table 2). In cases of risk of dental infection due to pulpal involvement and if time does not allow healing after a surgical procedure, root canal treatment may be considered if the periodontal status of the tooth is not compromised. For impacted teeth including third molars, failed endodontics and retained root tips, the treatment principles are similar to those outlined above and as summarized in Table 2. Other conditions such as partly erupted teeth with pericoronitis and history of symptomatic infection may require extraction based on the presence of infection, especially if symptomatic in the prior six months and if the systemic condition of the host allows and sufficient healing time is anticipated.[51,59]

A.7 Root canal treatment

Root canal treatment in symptomatic (painful) non-vital teeth can be considered if retention of the tooth appears critical for future dental care, as an outcome of endodontics cannot be determined with short periods of time before HSCT.[39] Definitive treatment is extraction (Table 2). Post extraction antibiotic coverage is provided, depending upon patients' white cell count and immunologic status and presence or absence of local infection. Endodontic treatment of asymptomatic non-vital teeth may be delayed until the hematological status of the patient becomes stable.[40] In cases with signs of infection and neutropenia (e.g. neutrophil count > 5.00/µl), antibiotics may be indicated.[16] If a periapical lesion is associated with an endodontically treated tooth without evidence of local infection, retreatment or extraction may not be required since the lesion may represent an apical scar or cyst.[16]

A.8 Prostheses and peri-implantitis

Poorly-fitting oral appliances can traumatize oral mucosa and increase the risk of microbial invasion into deeper tissues. The appliances should be removed and used only for dietary and esthetic purposes. Removable appliances and retainers that fit well may be worn as long as tolerated by the patient who maintains good oral care, although it is often recommended that removable prostheses should be removed at night. Patients should be instructed to clean their oral appliance twice daily using an antimicrobial solution to reduce microbial colonization of the device.[23]

Peri-implantitis is defined as an infectious disease causing an inflammatory reaction associated with loss of supporting bone around a dental implant. Mechanical debridement and improving oral hygiene are critical in management. Identifying and eliminating iatrogenic factors such as faulty restorations and residual cement, as well assessing parafunctional habits and occlusal overload are essential. The combined use of non-surgical care and chlorhexidine may be effective in reducing signs and pocket depth, but surgical inventions and local and/or systemic antibiotics may be indicated, and current recommendations are parallel to those for teeth (Table 2).[1,24] In the presence of extensive bone loss or implant mobility, the implant should be removed. As mentioned above, all surgical interventions should be planned in consultation with the transplant team and allow sufficient healing time. There is a lack of literature on the peri-implantitis and its management in the HSCT patients.

Table 2 Extraction guidelines for HSCT patients

Consider extraction	Dental extraction guidelines
Purulence on probing Periapical infection/inflammation Non-restorable/non-functional broken teeth Pocket depth ≥ 6 mm, and/or severe furcation defects* Excessive dental mobility Partially impacted teeth or retained roots at risk of infection Tooth with pericoronitis Tooth associated with malignant osseous disease	Potential surgical treatment coordinated with transplant team; may benefit from input of experienced dental professionals Consider prophylactic antibiotic after consultation with HSCT team Minimal trauma Smoothing sharp edge (alveoplasty) at least 7 days before chemotherapy Avoid intra-alveolar hemostatic packing agents

* When dealing with patients with periodontal disease of variable severities, dentists must often choose between treating the involved tooth or indicating its extraction. In non-cancer patients, criteria have been adopted in decision-making such as distribution, type and degree of bone loss, probing depth, attachment loss, presence and severity of furcation lesions, mobility, pulp involvement, occlusal aspects, in addition to factors related to the patient, such as age, systemic status, oral hygiene. (Moreira CHC, Zanatta FB, Antoniazzi R, Meneguetti PC, Rösing CK. Criteria adopted by dentists to indicate the extraction of periodontally involved teeth. J Appl Oral Sci 2007;15:437-441.) In transplant recipients, there is a lack of studies directed at this decision-making process, but factors such as the type of transplant (e.g. anticipated length of profound neutropenia and immunosuppression) as well as the available time to transplant, the patient's medical condition, and previous administration of antiresorptive medications may play a role.

Phase II: Conditioning and Neutropenic Phase

Phase II begins following initiation of transplant conditioning and continues to day +30 post-HSCT (Table 1), in which acute oral complications are related to the primary malignancy and the conditioning regimen. Common oral complications include: oral mucositis, oral pain, hyposalivation and xerostomia, secondary parotitis (in TBI), haemorrhage, opportunistic infections, taste dysfunction, neurotoxicity, dental pain, muscle tremors and temporomandibular dysfunction.[29] The patient should be followed closely to monitor and manage the oral changes and to reinforce the importance of optimal oral care.[56]

Dental procedures are usually not conducted in this phase unless considered a true medical emergency due to the patient's myelosuppression and immunosuppression. If emergency dental treatment is required, this will most often be managed by hospital-/cancer-center–based dental providers as part of the hematology/oncology team.

B.1 Oral hygiene

Intensive oral care is thought to reduce the risk of developing oral mucositis without causing an increase of fever or systemic infection and decreasing the oral microbial load may prevent infectious complications. Thrombocytopenia should not be seen as a reason to avoid oral hygiene, as gingivitis increases the risk of gingival bleeding; only if oral bleeding occurs following oral hygiene procedures should modification of oral hygiene be considered.

Prescription-strength fluoridated toothpaste should be used. However, if the patient does not tolerate use due to oral discomfort during the periods of oral mucositis, it may be replaced by mild-flavored toothpaste or gel (such as toothpaste manufactured for children or patients with dry mouth). If a regular soft toothbrush cannot be tolerated due to the severity of oral mucositis, super-soft toothbrushes with small, narrow brushheads may be more easily used. Brushes should be rinsed well and air dried between uses and regularly replaced. If foam brushes are used, they should be soaked in chlorhexidine prior to use to increase effect on plaque control; without the addition of chlorhexidine, the foam brush does not effectively reduce plaque levels.[21] Electric or ultrasonic toothbrushes can be used if the patient is capable of using them without causing local trauma and irritation.[10] If patients are skilled at using additional plaque removal devices (e.g. on interproximal spaces, furcations, bridges, implants etc), they should continue using them.

Fluoridated gel, or applications of fluoride varnish for patients at risk of caries and xerostomia, may be recommended based on individual conditions. A brush-on technique is convenient, familiar, and simple, which may increase the likelihood of patient compliance with topical fluoride therapy.[56] Wax-based or lanolin-based creams and ointments are effective in moisturizing and protecting the lips, but petrolatum-based products should be avoided.[47] The patients may develop hyposalivation during this phase due to the conditioning regimens with or without total body radiation. Palliation with topical agents and replacement of lost saliva functions can be assisted by xylitol-based chewing gum or candy, lozenges, special dentifrices for oral dryness, saliva substitutes, frequent sipping of water, alcohol-free oral rinses, and oral wetting agents or moisturizers.[38]

B.2 Mucositis

Oral mucositis usually begins 7–10 days after the initiation of conditioning and may progress for two weeks or more after the end of conditioning.[11] The severity of oral mucositis depends upon HSCT conditioning, ongoing medical therapy, pre-conditioning oral condition and individual variation (Fig 1). Oral mucositis care currently focuses on alleviation of symptoms and reduction of secondary factors, which may worsen mucositis.[30, 44] The management of oral mucositis includes good oral hygiene, topical anesthetic/analgesic agents, non-medicated oral rinses (mucosal coating agents [e.g. Amphojel, Kaopectate, hydroxypropylmethylcellulose, sulcralfate]), film-forming agents (e.g. Zilactin, Gelclair, Mu-Gard), and nutritional support. However, limited evidence

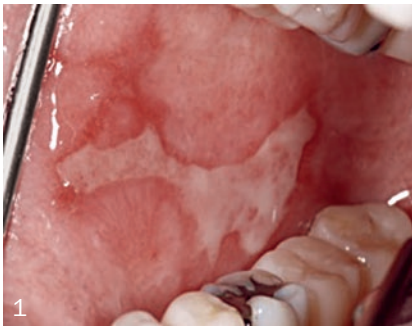


Fig 1 Oral mucositis involving buccal mucosa of a patient with chronic lymphocytic leukemia who underwent HSCT on day + 14.

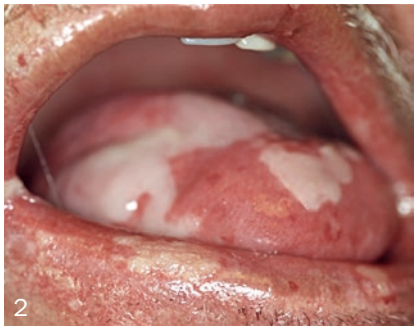


Fig 2 Oral mucositis involving dorsum and lateral border of tongue of a patient with refractory multiple myeloma who underwent HSCT on day + 11.

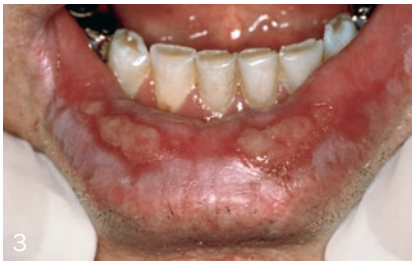


Fig 3 Recurrent labial herpes simplex in a patient with non-Hodgkin lymphoma on day + 7.

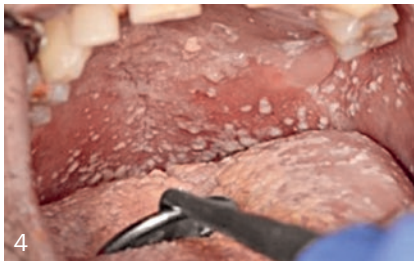


Fig 4 Oral candidiasis (thrush) in a patient with acute myelocytic lymphoma on day + 8.

supports coating, film-forming and barrier agents. Studies on the use of chlorhexidine for oral mucositis show conflicting results, with most showing no prophylactic impact; it is not recommended for oral mucositis prevention.[27,34]

The use of palifermin (keratinocyte growth factor-1) is recommended for the prevention of oral mucositis associated with autologous HSCT.[41,48] A more recent report suggested the effectiveness of palifermin in the allogeneic transplant setting.[37] Oral cryotherapy may reduce the incidence of severe oral mucositis after high-dose melphalan-based conditioning prior to HSCT.[19]

Low-level laser (photobiomodulation) therapy to decrease the severity and/or the duration of chemotherapy-induced oral mucositis is recommended in HSCT.[3,11,44] Novel therapies are under investigation.

Patient-controlled analgesia is helpful in managing pain associated with oral mucositis. There is limited evidence of the effectiveness or tolerability of mixtures containing topical anesthetics commonly known as 'magic mouthwash.'[44] Despite this, the use of topical anesthetics is commonly recommended for pain management. Topical anesthetics may dull or diminish the taste and gag reflex, and result in a burning sensation in addition to possible side effects in cardiovascular and central nervous systems.[2] Topical analgesics (e.g. doxepin and morphine compounded rinses) can be applied to oral mucosa for pain management with the advantage of a longer-lasting analgesic effect.[56] Systemic analgesics and systemic medications for neuropathic pain may play an important management of severe pain associated with oral mucositis. In allogeneic transplant patients, acute GVHD may occur following engraftment that occasionally involves the oral mucosa which may overlap with conditioning-induced oral mucositis.[29]

B.3 Oral mucosal infections

The clinical signs of inflammation and infection may be greatly diminished during neutropenic periods following HSCT, making recognition of infection more challenging.[22] Close monitoring and clinical suspicion allow for timely diagnosis and treatment of fungal, viral, and bacterial infections (Figs 3 and 4). It should be noted that although topical antifungal agents are commonly prescribed for their lower risk of side effects and drug interactions, the literature support of their efficacy is inconsistent.[28] Prophylactic mycostatin is not effective for the prevention or treatment of fungal infections, the taste and texture may be associated with nausea, and the sucrose content increases the risk of dental disease.[28] Fluconazole has become standard antifungal management, a common first choice with candida infection; however, it should be noted that increasing infection due to nonalbicans Candida and resistant albicans species may be resistant to fluconazole; identification and sensitivity profiling through microbiological analysis may be needed.

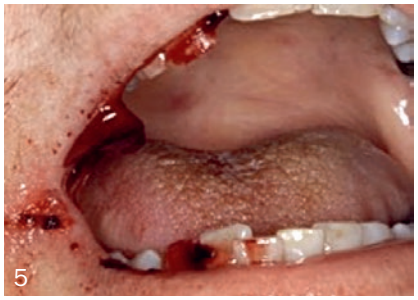
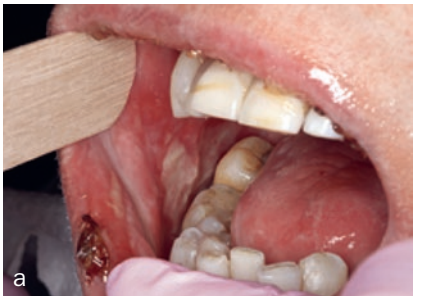
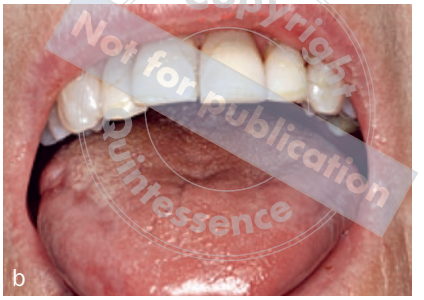


Fig 5 Spontaneous oral bleeding in a patient with acute lymphocytic leukemia on Day + 12 of HSCT.





Figs 6a and 6b GVHD in a patient with acute lymphocytic leukemia 6 months after HSCT.

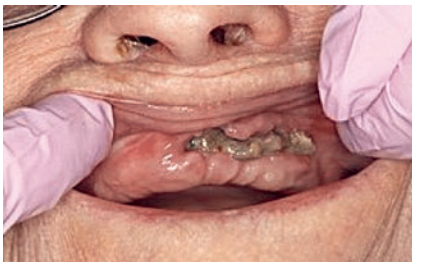


Fig 7 Medication-induced osteonecrosis of the jaw in a patient with multiple myeloma who underwent HSCT and was on Pamidronate for 2 years. The necrosis developed after the extraction of anterior maxillary incisors.

Periodontal diseases may be a source of systemic infection with few clinical findings in myelosuppressed patients. While erythema and pain may be reduced, tenderness may be present, therefore careful clinical evaluation including palpation and percussion is needed. Swabs, cultures or biopsies of suspicious lesions may be required for diagnosis. Empiric antimicrobials should be initiated until confirmation of the diagnosis and if infectious, microbial sensitivities.

B.4 Oral bleeding

Oral bleeding may occur due to thrombocytopenia, disturbance of coagulation factors and damaged vascular integrity, which is aggravated by mucosal damage and inflammation. If possible, treatment of the cause of tissue bleeding should be identified and addressed (Fig 5). Management of oral bleeding sites should consist of local approaches such as pressure application, antifibrinolytic rinses or topical agents. Systemic measures such as platelet transfusions should be coordinated with the HSCT team.[15]

Phase III. Supportive Care Following HSCT

Phase III continues from day +31 to day +100 post-HSCT (Table 1). Allogeneic-HSCT patients are often treated with immunosuppressive therapies based upon the risk of GVHD. During this period elective invasive dental care should be avoided, but oral hygiene measures should be reinforced. In case of a dental emergency, coordination with the transplant team is needed.

The oral status of the HSCT patients should be evaluated as part of the day +90–100 assessments, and every six months or at shorter intervals if there is a risk of hyposalivation, caries, oral GVHD and other toxicities or oral symptoms. Invasive surgical interventions should be avoided during this period and, if considered necessary, conducted only following consultation with the HSCT team.[6,20]

Dental symptoms can include temperature sensitivity, dental demineralization and dental breakdown. Comprehensive evaluation of changes associated with dental damage are needed and include evaluation of saliva production, oral hygiene, diet analysis, potential microbial shifts to a more cariogenic flora, and maintenance of dental mineralization are all needed. Topical application of neutral fluoride or desensitizing toothpaste helps reduce dental sensitivity, as well as the use of demineralizing products.[15]

C.1 Sensitivity / pain

Oral pain may be present due to dental and mucosal diseases and treatment effects. Dental sensitivity to intraoral thermal stimuli is often seen between two- and four-months post-transplant, although this may continue indefinitely. Tooth sensitivity may be related to decreased secretion of saliva, low salivary or local pH values, demineralization of tooth

structure and neuropathy. Management approaches include addressing dry mouth and topical interventions noted above.

Patients may be susceptible to local and systemic bacterial, fungal, and viral infections. Herpes virus infections (early HSV, later CMV, EBV, VZV) and Candida species are common. Prescribing chlorhexidine oral rinse as an adjunctive therapy in addition to strict daily oral hygiene will reduce oral bacterial and fungal loads. Thrombocytopenia (< 50,000/µl), if persisting, may present with gingival oozing, oral petechiae, hematoma, ecchymosis or spontaneous of bleeding requiring platelet support.[54]

Xerostomia/hyposalivation

Attention to the dental effects of hyposalivation is crucial.[10,15] For patients with xerostomia (subjective dry mouth), assessment of saliva production (at rest and stimulation) guides clinical decision making to address needs for systemic sialagogues. If no saliva production or no response to systemic sialagogues is seen, palliation with topical agents and replacement of lost saliva functions are sought. For example, it is recommended to use sorbitol- or xylitol-based chewing gum or candy, specific dentifrices for oral dryness, saliva substitutes, frequent sipping of water, alcohol-free oral rinses, and oral wetting agents or moisturizers.[38] Moreover, fluoride rinses and gels, and calcium-based remineralizing products and antimicrobials are recommended for caries prevention in high risk patients.

Phase IV: Immune Reconstitution / Recovery from Systemic Toxicity

Phase IV lasts from day +100 post-HSCT up to six to twelve months post treatment with overlap and one phase merges with another (Table 1). In this phase, the oral complications are predominantly related to the chronic toxicity associated with the conditioning regimen and ongoing medical care, and include salivary dysfunction/xerostomia, caries risk, taste change, mucosal sensitivity, craniofacial growth abnormalities, late fungal and viral infections, and oral chronic GVHD.[5,7,11,15,34] Relapse-related oral lesions may also be observed. Mucosal bacterial infections are rarely seen unless the patient is neutropenic or with severe chronic GVHD. GVHD is treated with local and/or systemic immunosuppressants and alleviation of pain. Periodic dental examinations with radiographs as indicated should be performed; however, invasive dental treatment should be avoided in patients with impairment of immune function, unless deemed urgent, and planned with the HSCT team.

Phase V: Long-Term Supportive Care Post HSCT

Phase V begins after day + 365 of HSCT (Table 1). The oral care of post-HSCT patients can be well managed in community dental practice using a multidisciplinary approach to support oral care. However, some unique and complex oral conditions may occur, requiring referral for expert diagnosis and management, including chronic GVHD, hyposalivation, taste change, mucosal sensitivity, oral squamous cell carcinoma, and other mucosal lesions. Routine non-invasive dental care (e.g. prophylaxis and simple restorative procedures) may be conducted. In the case of surgical or invasive procedures, consultation with the HSCT team may be appropriate. It is best to postpone elective dental treatments for twelve months post-allogeneic transplant if medical complexities are ongoing, certainly until the patient is hematologically stable (platelets > 50,000/µl^2, absolute neutrophils > 500/µl^2). Antibiotic prophylaxis may be recommended if invasive dental procedures are needed if absolute neutrophil count (ANC) is less than 500/µl^2 (Table 3). Control of bleeding can be achieved with atraumatic surgery, applying local pressure and additional surgical homeostatic techniques such as primary mucosal closure, pressure packs.[54]

E.1 Xerostomia/hyposalivation

Patients may have longstanding complaints of xerostomia because of the conditioning therapy, multiple medications commonly used in transplant care and potentially due to GVHD. The immunological response seen in GVHD can destroy the minor and major salivary glands. Also, changes in salivary composition may lead to increased viscosity and lower pH of saliva. These changes may also result in the reduction in remineralization of the teeth, tooth sensitivity and an increased incidence and severity of dental caries. Diagnostic tools such as measuring salivary flow rates and occasionally a salivary gland biopsy may be beneficial as an objective indicator for the presence and degree of GVHD,[10,15] which presents as periductal inflammation in the early stages and progressive acinar destruction and periductal fibrosis in the later stages.

Treatments such as encouraging good oral hygiene protocol, frequent hygiene visits, fluoride and remineralization supplementation, and sugarless chewing gum/salivary substitutes can help counteract these oral changes. Stimulation of residual salivary gland function may be accomplished with sialogogues or other approaches including photobiomodulation (low-level laser) therapy. Moreover, in a population with polypharmacy-induced xerostomia, daily use of topical palliative dry mouth products containing olive oil, xylitol, lipids, methylcellulose, and polysaccharides are shown to be safe and effective in relieving symptoms of dry mouth.[28,53] An increased risk of diabetes induced by medical therapy in HSCT represents a co-morbidity and may affect the oral status, including saliva production and infection risk.

E.2 Taste alterations

Taste change (dysgeusia) and decreased taste sensation (hypogeusia) are common in HSCT, which may be of short duration or persistent. Taste change can have a marked negative effect on oral intake, nutritional status and quality of life. Taste alteration may occur as a result of several factors, such as the malignant disease itself, medical management, neuropathy, hyposalivation, local infection and GVHD.[6] Current management focuses on dietary approaches with trials of medications that may affect appetite and taste (e.g. megestrol and cannabinoids). Zinc deficiency was found in some studies to be a potential factor in taste function, and zinc supplements have been reported to be helpful in radiation-induced taste dysfunction.[52] Taste,

Table 3 Management guidelines for invasive dental procedures and surgeries

Medical status	Guidelines available	
Patients with indwelling venous access lines (e.g. Hickman)	Low risk (based on AHA+)	There is no scientific proof detailing infectious risk for these lines following dental procedures.
ANC* > 1000/µl	No guideline available	
ANC > 500–1000/µl	Low risk	Liaise with the transplant team / dental experts. Clinical judgment and therefore experience are critical. If infection is present or unclear, more aggressive antibiotic therapy may be indicated.
ANC < 500/µl	Prophylactic antibiotics	Liaise with the transplant team. If microorganisms are known or suspected, appropriate adjustments should be based on sensitivities.
Platelets > 50,000/µl	No additional support needed	Major surgery may require platelet supplementation.
Platelets: 50,000–40,000/µl	Platelet transfusions are optional for non-invasive treatment. For surgical treatment (e.g. dental extractions), consider administering platelets preoperatively and 24 h later	Liaise with the transplant team. Platelet requirements will also depend on the extent of the surgery required / need for block injections. Utilise techniques to promote establishing and maintaining control of bleeding (i.e. sutures, pressure packs, minimise trauma).
Platelets < 40,000/µl	Platelets should be transfused 1 h before procedure. Obtain post-infusion platelet count; transfuse regularly to maintain counts >30,000– 40,000/µl until initial healing has occurred. In some instances, platelet counts >50,000/µl may be required.	Consider using haemostatic agents (i.e. microfibrillar collagen, topical thrombin). Tranexamic acid may help stabilise nondurable clots. Monitor extraction sites carefully for bleeding.

*Absolute neutrophil count; + American Heart Association.

smell, touch, temperature and visual appearance all have an impact on flavour, which plays a critical role in appetite and oral intake.

E.3 Graft versus host disease

GVHD is an immune response of the donor-derived immunocompetent cells to the host tissues, which can involve the lips, oral mucosa and periodontium, salivary glands and musculoskeletal tissue.[49] The severity depends on histocompatibility of the donor and recipient, age and gender of donor/recipient. Traditionally, acute and chronic GVHD have generally been distinguished by time of onset. Beginning within 90–100 days after stem cell infusion was considered acute, and onset after that date was considered chronic. However, based on the most recent NIH Consensus Criteria, clinical features determine whether the clinical syndrome of GVHD is considered acute or chronic, not the temporal relationship to transplantation.[25] Acute GVHD is a distinctive syndrome affecting the skin, gastrointestinal tract, and liver that rarely involves oral tissues. Chronic GVHD affects the skin, gastrointestinal tract, eyes, lungs, female genital tract and liver, and is common in the mouth.

Oral mucosal manifestations can be variable, including a white reticular network of lichenoid striae, diffuse white papules, atrophy, erosions, ulcerations and mucoceles of minor salivary glands (Fig 6).[52] Dry mouth may be present. Tongue, labial and buccal mucosae are commonly affected oral sites, although any oral surface may be affected. Its oral clinical features often mimic autoimmune conditions such as lichen planus and lupus erythematosus. Other oral findings include oral, head and neck soft tissue sclerosis. Using systemic or topical steroid agents (e.g. Clobetasol gel), topical immunosuppressant agents (e.g. tacrolimus ointment) and topical analgesic/anesthetic agents (see the mucosal pain in mucositis section) may alleviate symptomatic oral lesions.

E.4 Secondary malignancies

HSCT recipients are at risk of a higher incidence of selected malignant solid neoplasms including oral lymphoproliferative disorders, oral squamous cell carcinoma and salivary gland tumors.[9] Patients with long-term survival have a greater incidence of malignancy, in which risk factors include age at the time of HSCT (early age has an increased risk), total body irradiation, chemotherapy (e.g. azathioprine), acute or chronic GVHD, and duration of GVHD prophylaxis. Diagnosis of oral epithelial dysplasia and early squamous cell carcinoma arising in GVHD is often difficult, when GVHD camou-

flages and may even clinically mimic malignancy. Biopsy may be required for diagnosis. Regular oral soft tissue assessments during routine dental visits, especially with the presence of oral GVHD and early referral to an expert provider, will ensure early detection of oral lesions.

E.5 Osteonecrosis of the jaw

Some of the long-term medications required post HSCT, such as corticosteroids and bisphosphonates, have implications for oral findings and dental care. For example, patients with multiple myeloma are often treated with intravenous bisphosphonates and recently denosumab, which increases the risk of developing osteonecrosis of the jaw (Fig 7).[7] Elective invasive procedures should be avoided in these patients; if required, referral to an expert provider is recommended. Patients with a high risk of MRONJ are best co-managed with the HSCT team. Patients with delayed healing and necrosis should be referred to dental providers experienced in the management of necrosis, and particularly those who work with the HSCT team.

E.6 Gingival changes and oral lesions

Other potential oral complications of HSCT include gingival hyperplasia and oral granulomatous lesions.[15] Oral granulomatous lesions, such as pyogenic granuloma, have been reported in patients with chronic GVHD.[10] Gingival and other sites of atrophic change may be seen.

PEDIATRIC CONSIDERATIONS

Children receiving HSCT are at risk for oral complications during all phases of transplant. Children in whom tooth development is ongoing during cancer therapy have a high risk of dental developmental problems. Dental agenesis, microdontia, crown or root disturbances may occur. The severity of these dental developmental issues depends on the age and stage of development during treatment. Dental treatment for these anomalies may require a multidisciplinary approach. When a patient is more than two years post HSCT and disease free, treatments including orthodontics may be considered if indicated. Until immune recovery, elective invasive procedures should be coordinated with the transplant team.[2,54]

CONCLUSION

Oral and care should be recognised as critical prior to, during and after HSCT therapy. This review intended to provide recommendations for oral care throughout the HSCT continuum. Integrated multidisciplinary teams including dental professionals in cancer centers should guide the care throughout the early transplant period and consult with community providers for ongoing patient care. These clinical practice recommendations are provided for the transplant continuum described as five phases of HSCT care, based on the currently available literature and expert opinion. The contribution of dental professionals with expertise in HSCT procedures is considered of key importance to ensure success in oral care and complication management in HSCT recipients.

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