Disease/Medical Condition

BONE MARROW TRANSPLANTATION AND BLOOD STEM CELL TRANSPLANTATION
(also known as “BMT”; “BSCT”, “peripheral blood stem cell transplantation”, and “hematopoietic stem cell transplantation”)

Note: Further information on myelosuppressive chemotherapy and radiation therapy is found in the Chemotherapy Fact Sheet and the Radiation Therapy Fact Sheet.

Is the initiation of non-invasive dental hygiene procedures* contra-indicated? Possibly (e.g., during period of patient/client confinement in the transplant centre)

- Is medical consult advised? Yes, the patient/client’s oncologist/transplantation specialist should be consulted before any oral health procedure, including prophylaxis. This includes overall risk assessment and the safest time to schedule an appointment. Consultation should also occur if the patient/client is experiencing oral ulcerations and pain, is suspected of having active infection, or is suspected of having elevated bleeding tendency. Additionally, medical consult should occur if graft-versus-host disease or second malignancy in the oral region is suspected post-transplantation.

Is the initiation of invasive dental hygiene procedures contra-indicated?** Yes. Active chemoradiation therapy may affect appropriateness or safety, and scaling and root planing, including curetting of surrounding tissue, are contraindicated until the patient/client is medically cleared. In some cases, immunosuppression that warrants antibiotic prophylaxis and/or a bleeding disorder (thrombocytopenia) may be present.

- Is medical consult advised? As above. Specifically, the oncologist/transplantation specialist should be consulted regarding the status of blood counts (white and red cells), platelets, and clotting factors. If dental/dental hygiene procedures are absolutely necessary during the period of myelosuppression, consideration should be given to supportive measures such as administration of immunoglobulin G, adjustment of steroid dosing, and/or transfusion of platelets (in addition to antibiotic prophylaxis).

- Is medical clearance required? Yes. Inappropriately timed dental hygiene (and dental) procedures in an immunosuppressed patient/client can result in bacteremia, potentially leading to sepsis and even death. As well, bleeding risk needs to be assessed. During high dose chemotherapy +/- total body irradiation for BMT/BSCT, invasive dental hygiene treatment should be undertaken only on an emergency basis (and with appropriate precautions). Blood work should be conducted 24 hours before dental hygiene treatment to determine if the patient/client’s platelet count, clotting factors, and absolute neutrophil count are sufficient to prevent hemorrhage and infection.

- Is antibiotic prophylaxis required? Possibly, if invasive procedures are needed during the period of chemoradiation-induced myelosuppression. Prophylactic antibiotics may be recommended if the white blood cell (WBC) count is <2000/μL, or the neutrophil count is <1000/μL (500/μL in some institutions). As well, immunosuppressive drugs are used to manage complications resulting from transplantation, such as graft-versus-host disease (GVHD); antibiotic prophylaxis may be a consideration in these situations.

- Is postponing treatment advised? Yes. Elective oral procedures, including scaling and polishing, should be delayed until the patient/client’s immune system returns to normal; typically this takes 6-12 months post-transplantation. In patients/clients undergoing high dose chemotherapy +/- total body irradiation that results in:
  - immunosuppression, elective invasive procedures should be deferred until after chemoradiation-induced immunosuppression ceases. Specifically, treatment should be postponed until the patient/client’s absolute neutrophil count is >1000/μL and granulocyte count is >2000/μL to reduce risk of infection. Patients/clients who are neutropenic should not undergo invasive dental hygiene procedures without special precautions.
  - thrombocytopenia, elective invasive procedures should be deferred until a platelet count of at least 50,000/μL has been achieved in order to reduce the risk of bleeding.

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1 Granulocytes are certain specialized white blood cells, including neutrophils, basophils, and eosinophils.
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**Oral management implications**

- **Before transplantation**, all dental hygiene (and dental) treatment should be accomplished, because the patient/client will not be allowed to leave the transplant centre until the bone marrow has engrafted and blood counts have returned to a safe range. Therefore, all patients/clients scheduled for BMT or BSCT should undergo a pre-treatment oral health examination, which includes looking for infections on the tongue and oral mucosa.

- The dental hygienist should ensure the patient/client follows the prescribed oral hygiene regimen and fluoride gel application schedule. When the patient/client is scheduled for total body irradiation for BMT, custom fluoride gel trays should be fabricated for daily application of fluoride gel to prevent rampant dental caries.

- Oral surgery or other invasive procedures should be performed at least 7–10 days before myelosuppressive therapy begins.

- **During BMT/BSCT**, oral devices should be managed as follows:
  - brackets, wires and retainers should be removed before high dose chemotherapy begins;
  - dentures should only be worn when eating during the first 3–4 weeks after the transplant;
  - dentures should be rigorously cleaned;
  - mouth cleaning should occur with dentures or other oral devices out of the mouth; and
  - removable oral devices should not be used until mouth sores have healed.

- Many oncology/transplant centres adopt the strategy that the benefits of properly performed dental brushing and flossing in reducing risk of gingival infection outweigh the risks, although some centres have patients/clients discontinue brushing and flossing when peripheral blood components decrease below defined thresholds (e.g., platelets <30,000/mm$^3$ or <40,000 mm$^3$).

- In transplant patients/clients receiving high dose chemo that results in thrombocytopenia, vigorous teeth brushing should be avoided, along with water-irrigating appliances, and toothpicks. However, with appropriate monitoring, patients/clients can often brush and floss throughout the thrombocytopenic episode.

- Holding ice chips in the mouth during high dose chemotherapy may help prevent mouth sores.

- **Mucositis can be minimized by meticulous oral hygiene and other supportive measures.** This is important because this condition can increase the risk of systemic infection, promote oral hemorrhage, compromise the upper airway, and necessitate total parenteral nutrition.

- Once mucositis has developed, its severity and the patient/client’s hematologic status determine appropriate oral management. Some established guidelines for oral care include oral assessments twice daily for hospitalized patients/clients and frequent oral care (minimum of every 4 hours and at bedtime) that increases in frequency as the severity of mucositis increases.

- Oral care protocols generally includeatraumatically cleansing the oral mucosa, maintaining lubrication of the oral tissues, and relieving pain and inflammation. More specific management of chemotherapy-induced mucositis is contained in the Chemotherapy Fact Sheet, and management of dry mouth is covered in the Xerostomia Fact Sheet.

- Preventing dryness of the lips to reduce risk for tissue injury is important in transplant patients. Lanolin-based creams and ointments may be particularly effective in moisturizing/lubricating the lips and thus protecting against trauma.

- After transplantation, the dental hygienist should ensure adequate monitoring and control of plaque, tooth demineralization, caries, and infection.

- Elective invasive oral procedures should be delayed 6 to 12 months.

- The patient/client should be followed carefully for long-term oral complications, which may indicate graft-versus-host disease or malignancies in the oral region.

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2 An allogenic transplant recipient is typically hospitalized for 4 to 6 weeks.
3 Total parenteral nutrition (TPN) is exclusive feeding of a person intravenously, bypassing the usual process of eating and digestion.
Oral manifestations

■ Oral complications occur in most bone marrow and stem cell transplant recipients, and especially in patient/clients with graft-versus-host disease (GVHD).

■ Due to the cytotoxic and immunosuppressive effects of chemoradiation conditioning, patients/clients are prone to oral complications during the first month post-transplant. These manifestations include xerostomia, mucositis, stomatitis, ulcerations, bleeding, and infection. Although these side effects begin to resolve when hematologic status improves (typically decreasing in frequency and severity about 3 to 4 weeks after cessation of chemotherapy), immunosuppression may last for up to a year after transplant, and thus risk of complications continues.

■ Mucositis manifests as erythema and/or ulcerations. Often severe, it typically appears 7 to 10 days after initiation of high dose chemotherapy or chemoradiation for BMT/BSCT. The mucositis is self-limited when uncomplicated by infection, and it typically heals within 2 to 4 weeks after cessation of cytotoxic chemotherapy.

■ Bleeding problems due to thrombocytopenia (abnormally low platelet count) can occur in BMT and BSCT patients/clients undergoing total body irradiation. Gingival bleeding and submucosal hemorrhage can occur as a result of minor trauma (such as tongue biting or toothbrushing) when the platelet count falls below 50,000 cells/mm$^3$, and spontaneous gingival bleeding may occur with a platelet count < 20,000/mm$^3$, especially when there is pre-existing periodontitis or gingivitis. Although usually not serious, oral bleeding can be of great concern to the patient/client and family. The bleeding may be mild (e.g., petechiae or purpura located on the lips, soft palate, floor of the mouth, or lateral tongue) or severe (e.g., persistent gingival hemorrhage from herpes simplex virus ulcers in the presence of severe thrombocytopenia).

■ Herpes simplex and Candida albicans are common oral infections post-transplantation.

■ Dry lips may result from mouth breathing and/or xerostomia (sometimes secondary to anticholinergic medications used for management of nausea).

■ Temporomandibular joint dysfunction — manifesting as TMJ pain, headache, and jaw pain — may occur during the various phases of BMT/BSCT. Neurotoxicity — manifesting as muscle tremor (e.g., jaws, tongue) — may occur during the neutropenic and engraftment phases.

4 Petechiae and purpura are red or purple spots on the mucosa or skin, which do not blanch to applied pressure, caused by extravasation of blood (i.e., hemorrhages). Petechiae are pinpoint to pinhead in size (i.e., 1 to < 3 mm in diameter), whereas purpura lesions range from 3 to 10 mm in diameter.
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Oral manifestations (cont’d)

- After the first 100 days post-transplantation, patients/clients with no evidence of graft-versus-host-disease (GVHD) usually do not have oral complaints except varying degrees of xerostomia.

- Dental hypersensitivity may occasionally arise in patients/clients weeks or months after they discontinue high dose chemotherapy. Furthermore, patients/clients being treated with cyclosporine for treatment of graft-versus-host disease may report increased thermal sensitivity, which resolves after discontinuation of therapy (although it can persist for several months).

- Graft-versus-host disease (GVHD) often involves the oral cavity and salivary glands in allograft recipients. Oral manifestations include:
  - mucosal erythema and erosions/ulcerations, which appear in the mouth as early as 2 to 3 weeks post-transplant;
  - dry mouth;
  - dry lips;
  - pain from spices, alcohol, or flavouring agents (e.g., mint in toothpaste);
  - feeling of tightness in the perioral skin or in the mucosa of the mouth; and
  - taste changes.

- Chronic oral GVHD changes can manifest as early as day 70 post-transplant. These include persistent reduced salivary function (often with associated severe caries and tooth demineralization) and raised white hyperkeratotic plaques and striae. Patients/clients may also suffer from odynophagia (painful swallowing) and dysphagia (difficulty swallowing) due to gastrointestinal involvement.

- Submucosal and/or dermal fibrosis can occur in persistent cases of chronic GVHD. This scleroderma-like complication can manifest as slight mucosal or skin tightness, or it can progress to skin thickening and fibrosis. Intraoral submucosal fibrotic bands can significantly restrict the ability to open the mouth.

- Oral GVHD is linked to oral pre-cancerous and malignant lesions.

- Gingival hyperplasia can result from use of cyclosporine (a key anti-rejection drug for transplant patients/clients, which is also used to treat GVHD).

- Dental/skeletal growth and development alterations may occur in pediatric patients/clients in the immune reconstitution (late post-transplant) and long-term survival phases of BSCT.

- Oral squamous cell cancer is the most common second oral cancer in transplant patients/clients, with the lips and tongue being most commonly affected. Multiple myeloma patients/clients who have received a stem cell transplant using their own (autologous) stem cells sometimes develop an oral plasmacytoma.

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5 An allograft is the transplant of tissue or an organ from one person to another with a different genotype (i.e., not identical twins).

6 A plasmacytoma is a discrete, solitary mass of malignant plasma cells (white blood cells – lymphocytes – that produce antibodies) in either bone or soft tissue. In the oral cavity, it most commonly manifests as localized pain and as a raised lesion on the alveolar ridge (especially in the posterior mandible.) A radiolucency is typically seen on a radiograph when there is bone involvement.

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Related signs and symptoms

- Bone marrow transplantation and blood stem cell transplantation are used to treat certain cancers (e.g., some acute and chronic leukemias; lymphomas, including Hodgkin’s disease; neuroblastoma), as well as some non-malignant conditions (e.g., aplastic anemia and some genetic diseases, such as immunodeficiency syndromes and Hurler syndrome). BMT involves transfer of bone marrow into the patient/client, whereas BSCT involves the transfer of peripheral blood stem cells.

- Autologous stem cell transplantation is used to treat multiple myeloma.

- Prior to intravenously infusing a donor’s marrow or stem cells into the recipient’s blood, most recipients require immunosuppressive ablation of their own bone marrow so they will not reject the graft. This pre-operative preparation is accomplished by high dose, myelosuppressive chemotherapy +/- total body irradiation. In the treatment of malignancy, chemoradiation is also intended to destroy the cancer cells.

- Before the marrow/stem cell grafting procedure begins, most patients/clients experience a period of no marrow function as a consequence of the immunosuppressive preparation and their underlying disease. After the transplant, 10 to 28 days (the “critical period”) are required before the transplanted marrow/stem cells have sufficiently engrafted to begin to produce new marrow.

- The post-transplantation period has three phases: the pancytopenic/neutropenic phase; the immune recovery phase (3 to 12 months); and the long-term immunocompetent phase (1 to 3 years). The patient/client is at risk of complications (including infection, bleeding, and anemia) during the period of chemoradiation-induced myelosuppression (particularly during the immunosuppressive preparation and the first 28 days post-transplant), as well as afterwards if graft-versus-host disease occurs. Most patients/clients are given anti-rejection drugs (such as cyclosporine, methotrexate, or steroids) after transplantation. Antifungal drugs (e.g., intravenous miconazole) are also often given during immunosuppressive preparation and during the critical period after BMT/BSCT. Long-term therapy with broad-spectrum antibiotics is often needed to reduce the risk of infection.

- Upon full bone marrow recovery, signs/symptoms associated with acute cytotoxicity, immunosuppression, and thrombocytopenia disappear.

- Hypertension, bleeding problems, and anemia can result from cyclosporine-induced kidney and liver changes. Cyclosporine is also associated with hirsutism, gynecomastia, and cancers of the skin and cervix.

- Diabetes mellitus, hypertension, osteoporosis, impaired healing, increased risk of infection, and depression are side effects of prednisone (steroid) therapy. Adrenal gland suppression may also occur, which reduces the patient/client’s ability to deal with the stress of trauma, infection, or extreme anxiety.

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7 Hurler syndrome is a genetic disorder in which an enzyme deficiency results in the build-up of sugar molecules called glycosaminoglycans (formerly called mucopolysaccharides).
8 An autologous bone marrow graft involves transplantation of the patient/client’s own marrow, which was harvested prior to intense chemotherapy or total body irradiation used to prepare for transplantation. An allogenic marrow graft involves a donor and a recipient of different genetic origins, who may be related (e.g., sibling or parent) or unrelated.
9 Autologous stem cells are the patient’s own stem cells.
10 Multiple myeloma is a systemic, malignant proliferation of plasma cells that cause destructive bone lesions.
11 The recipient of a syngeneic marrow graft (from an identical twin) requires no immunosuppressive preparation, nor does the patient/client with severe immunologic deficiency (because of the very nature of the disease).
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Related signs and symptoms

- Graft-versus-host disease (GVHD) occurs when a patient/client’s tissue reacts to bone marrow or stem cells that come from another (non-identical twin) individual. Acute GVHD occurs within the first 100 days after transplant, and is characterized by dermatitis, non-infectious hepatitis, and intestinal inflammation (usually accompanied by diarrhea). Chronic GVHD usually occurs after the first 100 days, and it has manifestations similar to those of autoimmune disorders. These include keratoconjunctivitis, skin diseases, esophageal and vaginal strictures, pulmonary insufficiency, intestinal problems, and chronic liver disease. Both types of GVHD can result in fatal infections, and their various oral and gastrointestinal manifestations may lead to weight loss and malnutrition.

- Second malignancies later in life may be sequelae of bone marrow and stem cell transplantation.

References and sources of more detailed information

- Canadian Cancer Society

- Leukemia and Lymphoma Society of Canada

- Cancer Research UK


- D Saunders. Question 2 – What should I know about treating dental patients who are undergoing chemotherapy and when is the best time for dental treatment? Point of Care in JCDA March 2005;71(3):194-195.

- National Cancer Institute, National Institutes of Health: Oral Complications of Chemotherapy and Head/Neck Radiation (PDQ™)
  - Managing Oral Complications of High-Dose Chemotherapy and/or Stem Cell Transplant
    http://www.cancer.gov/about-cancer/treatment/side-effects/mouth-throat/oral-complications-pdq#section/_21
  - Oral Complications and Their Causes

12 GVHD often mimics autoimmune diseases such as Sjögren’s syndrome, scleroderma, pemphigus, and erosive lichen planus.

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<td>■ American Cancer Society <a href="http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/chemotherapy/understandingchemotherapypag%D0%B5forpatientsandsfamilies/understanding-chemotherapy-chemo-side-effects">link</a></td>
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* Includes oral hygiene instruction, fitting a mouth guard, taking an impression, etc.
** Ontario Regulation 501/07 made under the Dental Hygiene Act, 1991. Invasive dental hygiene procedures are scaling teeth and root planing, including curetting surrounding tissue.

Date: February 15, 2016