Pediatric bone marrow transplantation: oral complications and recommendations for care

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Abstract

Bone marrow transplantation (BMT) has become an increasingly common treatment option for those patients who have a disease that affects the bone marrow (BM) directly or indirectly. Because of the level of immunosuppression achieved in BMT, any problems the pediatric patient presents in the oral cavity can become life-threatening and increase the length of hospital stay, the patient's discomfort, and the treatment costs.

The oral cavity is a reservoir for microorganisms thus by reducing their number through optimal care, immunosuppressed patients may decrease their chance of a life-threatening systemic infection from an oral source. Many BMT teams believe that toothbrushing increases the risk of bacteremia and bleeding; however, problems are more likely to arise when patients are not compliant with good oral hygiene habits. It is vital to educate the caretaker and the child about the importance of oral care in order to minimize discomfort and maximize the chances for a successful transplant.

This paper discusses the important and unique role that pediatric dentistry has in the multiprofessional BMT team to help bring about a successful outcome through the prevention and treatment of the acute oral complications often seen in these patients. (Pediatr Dent 20:386–394, 1998)

A number of childhood disorders can affect the bone marrow (BM) and disturb the production of stem cells that give rise to blood and important elements of the immune system.[1–3] Bone marrow transplantation (BMT) has become the treatment of choice for those patients who have a disease that affects the BM directly or indirectly in which options for conventional therapy are likely to result in less successful disease-free survival.[3] Donor stem cells provide the recipient with new hemopoietic and immune systems. Because of the level of immunosuppression achieved in BMT, any problems the pediatric patient presents in the oral cavity can become life-threatening and increase the length of hospital stay, the patient's discomfort, and the treatment costs. The younger the patient, the more likely it seems that the chemotherapy affects the oral tissues probably because of the high mitotic index of oral mucosal cells in this age group.[4] In children under 12 years of age, more than 90% will show oral side effects.[4] The addition of total body irradiation (TBI) to the preparative conditioning only potentiates the problems. A sound initial consultation by a pediatric dentist to identify, treat, and prevent oral/dental problems and close monitoring of the soft tissues during the transplant course are vital to enhance the patient's chance for a successful outcome.

For didactic purposes, BMT was divided in four stages that correlate the procedure phases with the possible oral complications[5] (Table 1). The first section of

TABLE 1. STAGES OF BONE MARROW TRANSPLANTATION

Stage 1—Pretherapy	
	Patient and family education
	Eliminate/stabilize disease
Stage 2—Intratherapy	
(Day 0)	Conditioning
	Immunosuppression
	Continued recovery
	Mucositis, infection, hemorrhage, a-GVHD*
Stage 3—Post-therapy	
(Day +30)	Immunosuppression
	Continued recovery
	Mucositis, infection, hemorrhage, a/c-GVHD†
Stage 4—Long term	
(Day +100)	Immunosuppression to full recovery
	GVHD, xerostomia, late effects

*a-GVHD, acute graft vs. host disease.

† a/c-GVHD, acute chronic graft vs. host disease.

this article presents a brief overview of BMT and discusses the importance of a detailed oral/dental examination prior to the transplant (Stage 1). The second section (Stage 2) will review the oral complications and recommendations for treatment, emphasizing the important role of the pediatric dentist in the BMT team.

Bone marrow transplantation—an overview

BMT has been used to replace the marrow of patients with hematological malignancies (e.g., leukemia) or disorders (aplastic anemia, sickle cell anemia), congenital immunodeficiencies (severe combined immunodeficiency disorder, Wiskott-Aldrich syndrome), lipidoses (adrenoleukodystrophy) and inborn errors of metabolism (Hurler's disease).[1–3] It can also be used as a marrow support to allow the administration of higher doses of chemotherapy and/or radiotherapy in patients with solid tumors (e.g., neuroblastoma).[1–3] There are three main sources of stem cells used in BMT: multiple aspirations of bone marrow from the iliac crest, peripheral (circulating) blood, and umbilical cord blood (UCB).[3] Generally, patients with solid tumors receive autologous transplants using BM or peripheral blood stem cells (PBSC) whereas allogeneic BM or UCB are used in patients who have hematologic malignancies.[3] These cells can be collected from the patient him/herself (autologous transplant), from a donor related to the recipient, usually a parent or a sibling, or from an unrelated person (allogeneic transplant), from an identical twin (syngeneic transplant), and from a different species (xenogeneic transplant). If an autologous transplant is not feasible, the identification of a suitable donor becomes a major issue. Human leukocyte antigen (HLA) tissue typing is done to identify antigens located on the short arm of chromosome six of potential donors to match as closely as possible those of the recipient's (full or partial match).[2, 3, 6, 7] An autologous BMT has a much lower risk of transplant-related mortality (2 to 10%) and residual immunosuppression than do allogeneic (2 to 50%) or unrelated donor (40 to 60%) transplants.[7]

In preparation for the transplant, the patient receives high-dose chemotherapy alone or in combination with total body irradiation (TBI). The objectives of the conditioning regimen are to destroy the diseased marrow, to eradicate the patient's immune system in order for the donor graft to be accepted and to provide for "space" in the recipient's marrow cavity for the incoming graft.[2, 8] After the preparative conditioning, the white blood cells (WBC), granulocytes, red blood cells (RBC), and platelets rapidly fall and the patients need to be supported with RBC and platelet transfusions.[9] Evidence of engraftment will be detected between days 20 and 30, sometimes earlier, by increased peripheral WBC and platelet counts and is substantiated by the presence of donor cells on marrow aspirations.[9]

The pretransplant oral/dental evaluation (Stage 1)

The pediatric dentist's goals when evaluating a pre-BMT transplant are the identification, elimination, and prevention of potential problems that could deem the transplant unsuccessful. In doing so, the dentist should keep in mind the relevant principles that Pizzo and Schimpf[10] described to prevent or minimize the risk of infection in the oncology patient: bolster the host defense mechanisms, preserve the body's natural barriers of defense, reduce environmental organisms and minimize the endogenous microflora of the patient as a source of infection.

Review of the medical history

The patient's past medical history influences on the dental treatment planning and the efficiency of care delivery. The pediatric dentist should gather information about the underlying disease, time of the diagnosis, modalities of treatment the patient has received since the diagnosis (chemotherapy, radiotherapy, doses, ports, etc.) and complications. Surgeries, hospitalizations, emergency room visits, past episodes of infections (both oral and systemic), current hematological status, allergies, medications and a review of systems (heart, lungs, kidneys, etc.) should be noted. Details about the transplant should be reviewed such as type of transplant, donor, preparative regimen, graft-vs-host disease (GVHD) prophylaxis, etc. It is important to know that many pediatric medications used in BMT, such as

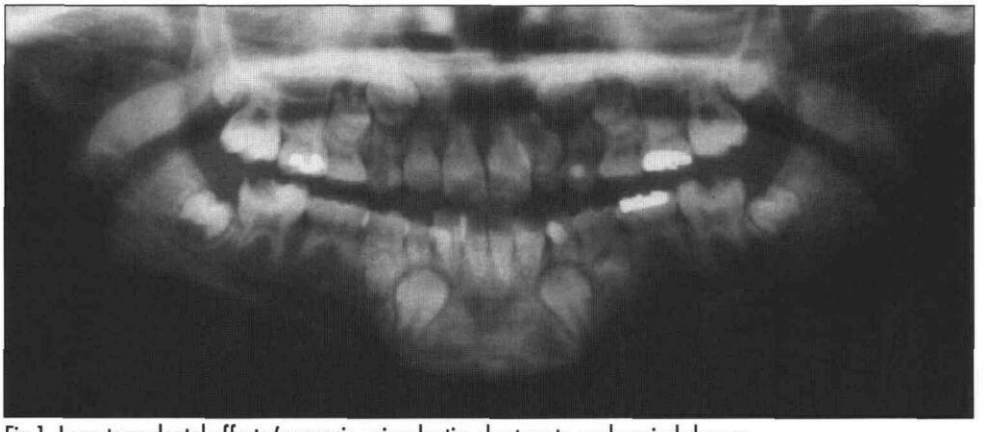

Fig 1. Long-term dental effects (agenesis, microdontia, short roots, early apical closure, small pulp chambers) seen in a patient treated with BMT at 3 years of age for acute lymphoblastic leukemia.

nystatin and clortrimazole troches, have high sugar content.[11, 12] This issue should be brought up to the attention of physicians, nurses and their assistants who often are not aware of the cariogenic potential of such products. Changes in the medication schedule should be made as possible to decrease the risk for dental caries; for example, ask the caretakers to not give the child clotrimazole troches before nap or bedtime.

The presence of a central line for venous access is common in these patients. The line is an indwelling catheter inserted into the right atrium through the subclavian, cephalic or jugular vein exiting the skin via a subcutaneous tunnel usually on the superior aspect of the chest.[13] Very young children may have the line exiting in their back to avoid their pulling it out intentionally. The device helps minimize frequent needle sticks and accidental leakage of chemotherapeutic agents into the veins, allowing multiple daily blood draws, administration of drugs, transfusion of blood products, parenteral nutrition, etc. The use of these access devices has improved the quality of life of the patients but it has also increased the risk for infections in the exit site and tunnel as well as catheter-bacteremia or fungemia.[13]

All patients who have central lines must receive antibiotic coverage according to the American Heart Association (AHA) guidelines before dental procedures that are likely to cause bleeding and bacteremia.[14] The pediatric dentist should not assume that, because pre-BMT patients are usually on prophylactic antibiotics, there is no need for extra coverage for dental procedures. The antibiotics that the patient is using may not protect against the bacteria that cause endocarditis.

Hematologic status

The dentist should be well versed in the interpretation of blood counts (Table 2). Two important parameters that should be known before any dental treatment are the number of platelets and the absolute neutrophil count (ANC).

Platelets are the blood elements responsible for coagulation. Thrombocytopenia refers to a platelet count of less than 100 000/mm^3 and is an expected complication of chemotherapy-induced myelosuppression. A moderate risk of bleeding exists when the platelet count reaches 50 000/mm^3.[15] Prolonged bleeding can also be caused by clotting and platelet disorders that are related to the baseline disease and to some drugs even though the platelet count may not be very low.[4, 15]

Neutropenia is defined as an ANC of less than 1500 cells/mm^3.[15] The incidence and severity of infection are inversely related to the number of neutrophils since they are the body's first line of defense. To calculate the ANC, take the differential blood count lab results, add the percentage of mature neutrophils (segs) and immature cells (bands) and multiply that percentage by the WBC count.[15] When the ANC is <1000/mm^3, elective dental work should be deferred because the risk for development of infections increases greatly.[16, 17] If a dental procedure is absolutely necessary, appropriate antibiotic coverage, beyond the AHA guidelines, should be discussed with the BMT team.

Identification of existing and potential sources of infections and problems

The patient's dental history should be reviewed and a thorough examination of the head, face, neck, intraoral soft and hard tissues should be performed, complemented by radiographs when indicated. A review of the patient's dietary habits, including bottle and breast feeding, should be done. Often times patients are given pediatric feeding liquids rich in carbohydrates which can make them high risk for caries. Bilateral parotitis can be seen, especially in patients who are undergoing or have just finished TBI. It usually resolves in 2–3 days and can be managed palliatively with ice pack applications.[5, 9] Partially erupted third molars can become a source of infection (pericoronitis) and should be evaluated and treated accordingly.[9] A panoramic film is an invaluable aid to assess dental developmental disturbances caused by past courses chemotherapy and/or radiotherapy and to anticipate future abnormalities (Fig1). [18–21] It should be attempted in all children who can cooperate with the procedure (usu-

TABLE 2. BLOOD COUNT NORMAL REFERENCE VALUES

Complete Blood Count	*Normal Value*
Hemoglobin (g/dL)	males: 14–18; females: 12–16 newborn: 16–19; children: 11–16
Hematocrit (%)	males: 40–54; females: 37–47 newborn: 49–54; children: 35–49
White blood cell count	5,000–10,000 cells/mm^3
Platelet count	150,000–400,000 cells/mm^3
Differential Blood Count	*Normal Value*
Neutrophils (Polymorphonuclear Leukocytes, PMNs)	50–70%
Lymphocytes	30–40%
Monocytes	3–7%
Eosinophils	0–5
Basophils	0–1%

ally from around 3 1/2 years of age on). It is recommended that a panoramic film be obtained annually after the transplant, especially for children who were transplanted before 7 years of age since the teeth were being actively formed during those years.

Dental treatment

During the first 6 months post-BMT, patients have profound impairment of most immune functions which may be fully restored by one year if chronic GVHD or other complications are not present. In GVHD patients, the immune reconstitution will be even more delayed.[6,9] Therefore, oral hygiene and dental rehabilitation should be as aggressive as possible before the transplant because the patients may not be able to experience any dental procedures for up to one year after the transplant.

Because of time constraints, the complexity of the patient's health, the implication of dental disease in the success of the transplant and behavior management issues, it is best that the dental consult be one of the first in the workup schedule. By doing so, enough time is allowed to coordinate the necessary dental treatment with the other numerous consultations and procedures that the patient will undergo in preparation for the BMT. Dental rehabilitation should be scheduled together with other medical procedures that require sedation or general anesthesia if possible (e.g., placement of a central line, lumbar punctures, biopsies, etc.) in order to provide timely and efficient care.

Studies[22,23] have shown that early and radical dental intervention reduces the frequency of oral problems in patients receiving chemotherapy and/or radiotherapy. Any active infection or potential sources of problems must be eliminated. Because of the low number of granulocytes in this period, swelling and purulent exudate may not be present, thus "masking" some of the classical signs of infections, leaving them clinically undetected.[9] The patient's general malaise, presence of fever of unknown origin, inflammation and tenderness in the oral cavity should raise suspicions of an ongoing infectious process. Development of fever in an immunosuppressed child requires prompt assessment and intervention with empirical antimicrobial therapy.[15,17] A good periapical radiograph is vital to determine dental abscesses in these situations.

Dental scaling and prophylaxis should be done and carious lesions should be taken care of promptly. Pulpotomies and pulpectomies in primary teeth are not advocated because failure of such procedures can lead to infection. In these cases, extraction is advised. Root tips, nonrestorable teeth and permanent teeth that need endodontic therapy which cannot be completed in a single visit should be removed as well.[4] Surgical procedures, including removal of third molars, need to be as atraumatic as possible, with no sharp bone edges remaining.[4] Satisfactory closure of the wounds must be obtained and chemoradiotherapy should be delayed, if possible, 4 to 7 days to allow for tissue healing.[5,9] Enamel fractures not necessitating full restoration should be smoothed to avoid irritation to the oral mucosa. Loose primary teeth should be left to exfoliate naturally; no complications are usually seen in those cases. Fixed orthodontic appliances and space maintainers need to be removed before the transplant conditioning starts because they can harbor food debris, compromise oral hygiene and act as mechanical irritants which can lead to open wounds and pain, increasing the risk for secondary infection. Removable appliances can be worn as long as tolerated if the patient shows good oral care.

Oral hygiene

The oral cavity is a reservoir for microorganisms thus by reducing their number through optimal care, the patients may decrease their chance of a life-threatening systemic infection from an oral source. Many BMT teams believe that toothbrushing increases the risk of bacteremia and bleeding, and advocate the discontinuation of oral hygiene with a regular brush particularly during neutropenic periods. However, problems are more likely to arise when immunosuppressed patients are not compliant with good oral hygiene habits since toothbrushing is the most effective means to remove plaque and to reduce gingival inflammation.[4,16,22,24–29] Thus it is important to educate the team members about the role of dental plaque in gingival inflammation and accumulation of bacteria. Sponges or foam brushes ("toothettes") and supersoft brushes are not effective to remove plaque and debris due to their softness, therefore their use is discouraged. It is recommended that, at this stage, toothbrushing be done at least twice daily with a regular soft brush. The use of a nonabrasive fluoridated toothpaste is advised. Flossing should be done once daily if it can be accomplished atraumatically by the patient or with the help of a caretaker. If flossing cannot be done skillfully, it should not be emphasized during this stage.

Rinses are also an important part of the oral hygiene protocol because they keep the tissues clean and moist and remove debris. Upon hospital admission, patients should rinse with normal saline or sodium bicarbonate solutions four to six times daily. These solutions are nonirritating to the mucosa, are economical, and readily available. If the young patient is not compliant with the rinses because of the taste, sterile or tap water can be used. As vomiting can happen frequently due to conditioning regimen toxicity, patients should be instructed to rinse after emesis episodes in order to prevent the stomach acid from irritating the oral tissues and decalcifying the teeth.[5] Although it is useful for removing oral debris and blood clots, hydrogen peroxide is not indicated because it tends to dispose of superinfection, to dry the oral mucosa and to delay the

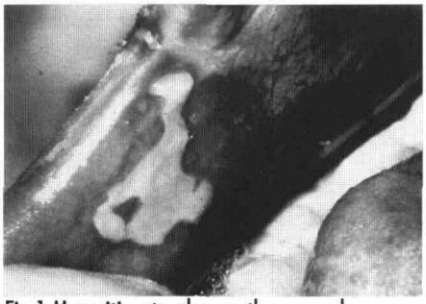

Fig 1.Mucositis: atrophy, erythema, and pseudomembrane on the buccal mucosa.

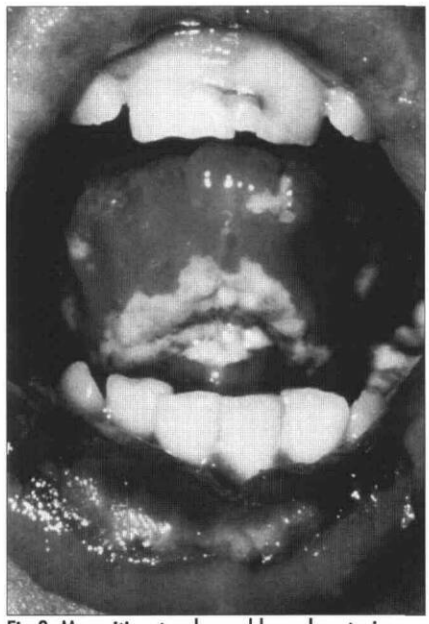

Fig 3. Mucositis: atrophy and hyperkeratosis on the tongue, bleeding and ulceration of the lower lip.

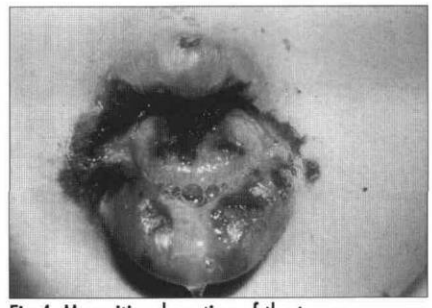

Fig 4. Mucositis: ulceration of the tongue and lips.

healing of newly formed tissue.[5, 16, 29] Furthermore, its foaming can lead to aspiration especially in patients whose gag reflex is compromised.[16]

Patients who present poor oral hygiene or periodontal problems can use chlorhexidine rinses once or twice daily up to the point when the gingival health has been restored or when the mucosa shows signs of the initial stages of mucositis (discussed in the second section of the article). Due to its strong bitter taste, the solution can be diluted a little to help with the child's compliance. Long-term use of chlorhexidine can cause extrinsic brownish staining in the teeth and tongue, alter the taste sensation and produce transient swelling of the parotid glands.[24, 30] Many products bind to chlorhexidine (e.g., toothpaste and medications) resulting in decreased efficacy which can be potentiated by the presence of necrotic debris and extensive plaques in the mouth.[31] Nystatin rinses and chlorhexidine, for instance, should be used at least 30 minutes apart in order to obtain the best action of both drugs.

Fluoride drops can be added to the rinses to provide protection against dental decay since many BMT teams do not allow the patients to drink tap water for a long period of time. Neutral fluoride rinses or gel applications are indicated for those patients who have experienced or are at risk for prolonged xerostomia, which is rare in BMT, except in cases where radiation is given directly to the salivary glands. The prescription of supplemental fluoride should be done according to the recommendations of the American Academy of Pediatric Dentistry.[32]

Education of patients and caretakers

It is vital to educate the caretaker and the child about the importance of oral care in order to minimize discomfort and maximize the chances for a successful transplant. When they understand the possible oral complications and their consequences, they are more likely to participate in the care and follow-up with the recommendations. Other topics for discussion should include, but not be limited to, dietary habits, potential cariogenic effects of some drugs used in the transplant, and late effects of the conditioning regimen on the craniofacial growth and dental development, especially in patients under 7 years of age. It is important for the pediatric dentist to realize that these issues are rarely discussed by the physicians and nurses involved in the patient's care.

Oral complications during the transplant and early engraftment period (Stage 2)

This section will present the management of oral complications that can occur from the beginning of the conditioning regimen (usually 7 to 10 days prior to the transplant itself) through the early engraftment period up to day 30 post-BMT. It is of paramount importance that the oral care protocol be clear to all the members of the team who are directly involved in patient care, especially the nursing staff, so that the recommendations can be implemented accordingly.

Mucositis

The agents used in the preparative regimen are not specifically targeted to malignant cells only and can largely affect tissues that have a rapid cell turnover such as the oral mucosa, inhibiting its basal layers to replace the superficial cells leading to a generalized mucosal inflammation (mucositis).[15, 16, 27, 33] The occurrence and severity of mucositis show great individual variability because it depends on drug doses, schedules, duration of treatment, and impairment of renal and hepatic function.[15] Tissue changes can be noticed between 4 and 7 days after the initiation of conditioning and generally last from 10 to 14 days.[5] In the initial stages, atrophy and generalized erythema occur and is most evident in the nonkeratinized surfaces of the buccal and labial mucosa, floor of the mouth, lateral and ventral tongue and soft palate (Figs 2, 3, and 4). Eventually the dorsal tongue, hard palate and gingiva may also show atrophic changes.[5, 9] The lateral borders of the tongue are usually the last sites to heal due to trauma from mastication and rubbing against the teeth (Fig 5).

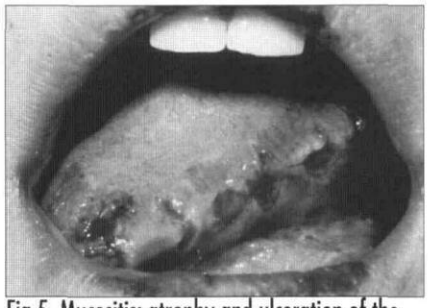

Fig 5. Mucositis: atrophy and ulceration of the lateral border of the tongue.

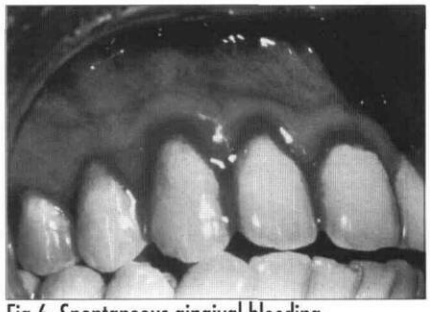

Fig 6. Spontaneous gingival bleeding.

A lot of morbidity, such as dysphagia, poor nutritional intake, increased discomfort, difficult speech, oral bleeding and secondary infections, can be seen. Severe mucositis in the pharynx can lead to intubation of the patient to protect the airway. The development and duration of neutropenia may be the most important single factor related to mucositis[34] so when resolution of neutropenia and engraftment start taking place, the oral mucosa status improves substantially.[35]

Pain management of mucositis

Mucositis management remains directed at symptomatic treatment, prevention of infection and trauma, with persistent and frequent use of strategies that enhance the patient's quality of life. Very young infants present a special challenge since they are not able to participate actively in the treatment. They are usually placed on intravenous narcotic analgesics to keep them comfortable. Children who are able to follow instructions are given a patient-controlled analgesia (PCA) device which allow self administration of sedative medications. Many times, however, other local palliative measures are necessary to help relieve the oropharyngeal pain. Viscous lidocaine hydrochloride (2%) and dyclonine hydrochloride (0.5 or 1.0%) are the most commonly recommended topical anesthetics. Because they are contact medications, the patients should rinse or bathe the oral tissues for at least 3 minutes, otherwise the desired effects will not be produced. Diluting the lidocaine a little with sterile water, for example, makes rinsing easier. Local anesthetics can also be applied topically with a cotton tip or a toothette if the child is not able to rinse and spit or has only a few painful ulcers. Gargling and swallowing are not advised since loss of gag reflex can bring about aspiration of saliva, mucous, loose tissues, etc.[5] Due to the short periods of relief they provide, patients can abuse the use of anesthetic solutions leading to high blood levels and systemic effects such as CNS depression and excitation and cardiovascular complications.[36] The rate of mucosal absorption of anesthetics is particularly rapid when open wounds and ulcerations are present. Therefore, patients should be instructed to use them with caution (not more than once every 30 minutes). If the patient is able to eat but has oral discomfort, he/she can swish with the anesthetic at least 20 minutes before the meal to decrease the chance of accidental trauma.

The use of antihistamines, topical anesthetics and antacids, alone or in combination, have been suggested but there is no experimental evidence to support the efficacy of one combination over another.[15, 35] The "swish and swallow" rinses that can anesthetize the oropharynx are discouraged due to the potential risk of aspiration. Coating agents (e.g., kaolin-pectin, magnesium hydroxide, sucralfate, hydroxypropylcellulose) can protect the mucosa and reduce irritation but some of them cause dryness and slow the absorption of topical oral medications.[4, 5, 36] Benzydamine hydrochloride, a nonsteroidal agent that has anti-inflammatory properties and is mildly anesthetic, seems to help accelerate the resolution of mucositis; however, it is not currently available in the US.[36] More recent strategies include the use of cryotherapy, oxpentifylline, prostaglandin E2, fibronectin, and epidermal growth factors.[37] Analgesics should be used according to the patient's level of pain, its pharmacologic action, and duration.[36]

Other practical measures to increase the comfort level include the use of ice packs on the cheeks and throat, popsicles, ice chips, and icy drinks. A bedside suction device, carefully used to avoid rubbing against the tissues and opening new wounds, is helpful to remove thick mucous and saliva. Often times mucositis will produce hyperkeratotic tissues which the child tends to pick causing bleeding, pain and ulcerations. If the platelet count is > 50,000/mm^3 have the patient swish with an anesthetic solution and carefully debride only the loose tissues using suture removal instruments. The lips must always be moist with water-based lubricants or those containing lanolin to keep it from cracking, bleeding and becoming a site for infection. A thin layer of lanolin applied with a cotton tip several times daily is recommended. Chronic use of oil-based products such as vaseline results in atrophy of epithelium and risk of infection under occlusion of application and thus should be avoided.[36]

Oral hygiene

Toothbrushing should continue as described in Stage 1 throughout the whole hospitalization course. Platelet numbers should not be the sole determinant of oral hygiene as patients are able to brush without bleeding at widely different levels of platelet count.[38] End-tufted brushes are particularly useful during mucositis if a regular brush cannot be tolerated. Sponges or foam brushes ("toothettes") are only advised as a last

resource for oral care due to their poor cleansing properties. Patients may complain of discomfort when using a toothpaste because of altered taste sensation. In that case, the toothpaste can be dismissed since the essential factor is the mechanical action of the brush itself. Flossing should not be emphasized, particularly for those patients who are not used to it and who have some degree of mucositis.

Rinses with tap or sterile water, normal saline or sodium bicarbonate should be done as often as possible to maintain the tissues clean and wet, remove debris, facilitate the expectoration of thick saliva and decrease the risk of opportunistic infections. An extra soothing effect on the mucosa is obtained when the rinse is kept ice cold. Fluoride drops[32] can be added to the rinses if the patient is not drinking fluoridated water. Studies on the efficacy of chlorhexidine in mucositis have drawn mixed conclusions.[24, 30, 33, 34, 39, 40] Its high alcohol content (11.6%) can burn the tissues, increase their dryness and delay healing.[9, 15, 24, 30, 39] Parents and nurses often report how much children complain when given chlorhexidine to rinse with during mucositis. Thus caution must be exercised in prescribing mouth rinses that contain alcohol during this stage of transplantation.

Oral bleeding

Oral manifestations of thrombocytopenia include bruising, petechiae, purpura, and oozing from mucosal surfaces which can be complicated by the presence of irritating factors (plaque, calculus, orthodontic bands, appliances, etc), ulceration, infections and some medications such as penicillins, amphotericin B, miconazole, aspirin, and nonsteroidal anti-inflammatory drugs.[15, 38] Spontaneous gingival bleeding can occur when platelets reach a level of 20 000/mm^3 or less (Fig 6).[4, 15] It requires expeditious intervention because it may be a sign of potentially fatal hemorrhages in the central nervous system, respiratory tract and gastrointestinal tract.[15] Elective surgical procedures and local anesthetic blocks should be avoided during thrombocytopenic periods. If a surgical procedure is absolutely necessary, the pediatric dentist should not proceed until clearance is given by the BMT team. Topical therapies, such as moist gauze pressure pack, ice packs and topical hemostatic agents (thrombin, microfibrillar collagen, epinephrine, etc) should be tried first.[5, 9, 15, 38] If bleeding becomes more severe, platelet transfusion is warranted. However, multiple platelet transfusions can sensitize the patient through the lysing of newly infused platelets by the circulating anti-HLA antibodies and complement hence they have to be planned carefully.[4]

Infections

Pre-existing infectious processes, acquisition of new pathogens, reactivation of latent microorganisms, constant use of antibiotics, xerostomia, breakdown of the oral mucosa, and prolonged myelosuppression and immunosuppression are factors that predispose the oral tissues to opportunistic infections.[9] Frequent oral exams while the patient is hospitalized allow for early recognition, diagnosis and quick intervention. *Candida albicans* is the most common causative organism of oral infection in the BMT patients.[4, 9] Its clinical appearance varies but most commonly it presents as raised, white curdy-looking areas involving any part of the oral cavity.[4] These white plaques can usually be scraped off revealing a raw bleeding base.[4] Patients can be treated with nystatin solutions and clotrimazole troches, both very rich in sucrose. Ketoconazole, miconazole and fluconazole are also used while intravenous amphotericin B is reserved for aggressive treatment of systemic and invasive infections.[4, 9] Aspergillus is the next common fungal isolate.[5]

Herpes simplex virus (HSV) is the most frequently observed viral pathogen in immunocompromised patients. Patients who test positive for HSV usually receive low dose acyclovir up to day 28 post-BMT to prevent reactivation of oral HSV which is the case in almost all of the herpetic episodes seen in BMT.[3, 41] However, resistance to acyclovir and breakthrough of infection despite its prophylactic use have been reported.[41] Oral HSV can contribute substantially to ulceration and bleeding and thus can be confused with mucositis; involvement of perioral tissues such as the lip and nose help in the clinical assessment.[9, 41] HSV infections show groups of vesicles that quickly breakdown leaving small ulcers that may coalesce.[9] They heal slowly and improvement is more likely to occur when the granulocyte count increases.[9] Systemic narcotics may be prescribed since pain from viral infection can be excruciating.[5, 41] Cytomegalovirus infection can happen in about 70–80% of patients who are seropositive if they do not receive prophylactic therapy with ganciclovir for at least 100 days post-BMT.[3, 42] They are generally not clinically apparent, making its diagnosis difficult.[42, 43] Oral bacterial infections are often nondescript and accurate diagnosis depends on cultures.[9] Their frequency is low due to the use of prophylactic antibiotics, dental and periodontal rehabilitation pre-BMT, and optimal oral hygiene.

Xerostomia and taste disturbances

The conditioning protocol can induce some degree of salivary dysfunction which can be further exaggerated with the use of oxygen support, medications with anticholinergic effects, GVHD and mouth breathing.[5,44] It is transient in the BMT patient and can last from a few weeks to several months, except in cases where radiation has been given directly to the salivary

glands.[5] The saliva becomes thick and viscous. Mastication, swallowing, speaking and taste become impaired, the oral mucosa can break easily, and colonization of microorganisms is facilitated.[5, 37] Salivary flow can be stimulated by chewing sugar-free gum and candy if tolerated. Optimal oral hygiene is vital, especially the frequent use of rinses. Consumption of sugar-free drinks and avoidance of a diet rich in sucrose and carbohydrate decrease the potential damage to the dentition. Foods that are coarse (e.g., french fries, pizza) and spicy should be avoided to protect the oral mucosa from further irritation and breakdown. Oral dryness can potentiate disturbances in taste and aversion to certain food odors. It is usually noticed after the transplant and can last for over 60 days.[5] Consultation with a nutritionist is helpful to identify foods with pleasant aromas that can stimulate the appetite and soothe an unsettled stomach in order to maintain an appropriate nutritional balance.[15]

Acute GVHD

GVHD is a process in which the transplanted T-lymphocytes recognize histocompatibility antigens of host tissues as foreign, causing injury in several parts of the body.[3, 7, 45] Acute GVHD occurs within the first 100 days post-BMT with a median onset on day 19.[3, 7] It is difficult to distinguish oral mucosal changes due to GVHD from those caused by other factors such as the conditioning regimen toxicity, post-BMT drugs (e.g., methotrexate) or secondary infections since they all have overlying periods and similar features.[7, 45, 46] The diagnosis of oral acute GVHD depends on the presence of systemic disease and the exclusion of other causes for the oral lesions. The most common oral changes related to GVHD are erythema (most frequently seen on the dorsal and ventral tongue, floor of the mouth, gingiva and labial mucosa) and lichenoid changes (labial and buccal mucosa, lateral tongue).[46] Atrophy, hyperkeratosis and ulcerations are less common. Oral acute GVHD should be suspected when mucosal changes appear, worsen, or persist beyond day 21 post-transplant, and there is subjective pain and dryness, especially after 4–5 weeks post-BMT.[7, 45] The use of prophylactic measures against systemic GVHD and its successful treatment reflect directly on the prevention and treatment of the oral form of the disease. Good oral hygiene, steroid rinses (dexamethasone), or gels (clobetasol, fluocinonide), treatment of concurrent oral infections, rinses (saline, sodium bicarbonate), and topical anesthetics are helpful palliative measures.[7, 45]

Neurotoxicity

Plant alkaloid drugs (vinblastine, vincristine) used in the conditioning regimen can produce peripheral neuropathy leading to complaints of jaw pain or toothache, particularly in the lower molars.[4, 15] A dental examination should be done to rule out odontogenic infections but in cases of neurotoxicity the exam will prove unremarkable. Treatment is palliative and the symptoms disappear a few days after discontinuation of the drug.[15]

Summary

BMT has become an increasingly common treatment option for a number of diseases and disorders. Because of previous treatment for the baseline disease, the type of preparative regimen for the transplant, GVHD prophylaxis and the resulting immunosuppression, transplant recipients often present oral problems ranging from minimal mucosal irritation and transient xerostomia to bleeding, pain and life-threatening infections. This paper discussed the unique role that pediatric dentistry has in the multi-professional BMT team to help bring about a successful outcome through the prevention and treatment of the acute oral complications often seen in these patients.

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