PERIODONTAL MANIFESTATIONS AND TREATMENT CONSIDERATIONS FOR ORGAN TRANSPLANT PATIENTS

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Abstract

The need for the dental evaluation of transplant patients before and after transplantation is increasing with the rise in number of transplants being performed. The evaluation is necessary to eliminate and/or treat active sites of infection in the oral cavity. Oral infections can increase the risk of systemic infections as a result of immunosuppression, which may lead to transplant rejection. In all these cases, dental protocols must be observed to provide safe and effective care for patients. This article briefly discusses the periodontal manifestations and treatment considerations for organ transplant patients.

Introduction

Organ transplantation is the transfer of an organ from one body to another or from a donor site on the patient’s body, for replacing the recipient’s damaged or absent
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organ. The most common organs transplanted are the kidney, liver, heart, lung, and pancreas. The kidney is the most commonly transplanted organ worldwide, followed closely by the liver and then the heart. Organ transplantation is often the only treatment for end-stage organ failure, such as liver and heart failure. Although transplantation is beneficial, it is not without complications, ranging from life-threatening infections to graft rejection. Dental infections and manipulation of oral tissues may subject immunosuppressed patients to infections, which can lead to organ rejection, dysfunction of other body systems, or even death.¹ All transplant patients are typically screened for adequate dental health before and after an elective organ transplant to eliminate or treat active sites of infection in the oral cavity.² In such cases, careful dental protocols must be observed to provide safe and effective care for patients. This article briefly discusses the periodontal manifestations and treatment considerations for organ transplant patients.

**Periodontal manifestations**

The psychological stress that organ transplant patients are preparing to undergo or have been undergoing results in poor oral hygiene, thereby compromising periodontal health. The periodontal manifestations found in transplant patients can be caused by immunosuppression; adverse effects of the immunosuppressive agents; and caused by graft-versus-host disease (GVHD) in patients undergoing hematopoietic cell transplantation. The long-term immunosuppressive therapy administered to these patients compromises their immune response, which makes them more susceptible to fungal, viral, or bacterial infections as well as infection with microorganisms commonly found in periodontal diseases. Patients may be particularly susceptible to necrotizing ulcerative gingivitis (NUG) and necrotizing stomatitis.³

Viral infections of the oral cavity have been a major concern in immunocompromised patients. Herpes simplex infection followed by chronic herpes is difficult to diagnose on the basis of clinical presentation alone. Hairy leukoplakia has been reported in organ transplant patients without human immunodeficiency virus infection.⁴ Varicella zoster virus and Epstein–Barr virus have been identified in oral lesions. Cytomegalovirus infection (CMV) is common in the first months after transplant. In addition, prolonged immunosuppression makes them more vulnerable to human herpes virus-8 infection. While viral infections in normal patients usually require symptomatic treatment, early diagnosis and prompt treatment with appropriate antiviral agents are required in the case of immunosuppressed patients.

Fungal infections have also been of concern in this group of patients. Candidiasis is the most common fungal infection and can
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present in any form or in combination with other fungal infections. Aspergillosis, mucormycosis, blastomycosis, and cryptococcosis are other fungal infections that can affect the oral cavity, individually or in combination with candidiasis. The standard “azole-type” treatment might be effective, and sometimes amphotericin B might also be required as part of the treatment.

Immunosuppressant drugs, such as cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, corticosteroids, and sirolimus, are usually prescribed in organ transplant patients. Cyclosporine causes gingival overgrowth that usually starts manifesting as early as 3 months into therapy. The most common area affected is the facial aspect of the maxillary anterior teeth. Gingival overgrowth as a result of cyclosporine can be preceded by pre-existing plaque-induced inflammation. Good oral hygiene has been shown to decrease the level of overgrowth. Gingival overgrowth interferes with the patient’s oral hygiene, leading to an increased susceptibility to infections, caries, and periodontal disease. Severe gingival overgrowth generally requires gingivectomy for definitive therapy. Biopsy of the excised gingival tissues has been recommended since malignant tumors and pemphigus vulgaris lesions are known to be associated with gingival overgrowth. Cyclosporine is also associated with an increased incidence of skin and oral squamous cell carcinoma, lymphoma, and Kaposi sarcoma. Tacrolimus is associated with less gingival overgrowth and can be used as a substitute for cyclosporine.

GVHD is a potentially life-threatening immunologic phenomenon that affects up to 45% of bone marrow transplantation patients. The disease occurs when acquired immunocompetent T-lymphocytes from the graft attack the host cells of the graft recipient. Acute lesions usually occur within the first month of engraftment. Target organs include the liver, lungs, and gastrointestinal tract. The exocrine glands, skin, and mucosa also may be affected, and the oral cavity is usually involved. The diagnosis of GVHD is based on abnormal liver function tests or the appearance of skin and mucosal lesions. A wide variety of oral changes may occur, ranging from mild mucosal erythema to severe mucositis. Gingivitis, desquamation of oral tissues, ulcerations, and xerostomia are common. Occasionally, a salivary retention phenomenon results in the formation of saliva-filled vesicles. Atypical pyogenic granulomas may occur in response to trauma. Oral signs and symptoms are similar to those encountered in lupus erythematosus, lichen planus, scleroderma, or Sjögren syndrome. Oral lesions are very difficult to treat and require change in the immunosuppression level, along with the topical application of cyclosporine or azathioprin. Xerostomia is a common feature (occurring as a result of radiation or chemotherapy along with mucositis) in
patients who have undergone hematopoietic cell transplantation. There is no definitive treatment of GVHD, although palliative medications, such as topical anesthetic in a mixture of an antihistamine and a coating agent, can be used.

Apart from infections, patients may also show noninfectious lesions, which may be representative of neoplasms. Transplant patients have been reported to develop lymphoma and Kaposi’s sarcoma in the mouth and squamous cell carcinoma in the lips. These conditions may be treated by altering the immunosuppressive regimen, along with chemotherapy and radiotherapy.

Before bone marrow transplantation (BMT), chemotherapy and total body irradiation are used to destroy the patient’s malignant marrow cells. The BMT recipient is extremely susceptible to opportunistic infections immediately after chemoradiation and infusion of donor marrow cells (pancytopenic phase). During the pancytopenic and recovery phase, the patient is at risk from even minor infections because of the presence of neutropenia. Because these chemotherapeutic agents may also destroy normal tissue cells that are metabolically active, the kidneys, heart, skin, immune system, and the gastrointestinal tract (including the oral cavity) may be adversely affected. Oral tissues are continually exposed to injury (physical, chemical, thermal, and microbial), and the mouth is often the primary site of complications associated with chemotheraphy. Xerostomia, dysphagia, altered taste perception, mucositis, soft tissue ulceration, and infection are common adverse oral effects. Onset of mucositis usually occurs within 5 to 7 days of the initiation of therapy, and the condition may last for days to weeks. Lesions may be more severe and last longer if combination drug therapy or chemoradiotherapy is used. Gingivitis may be the second most common oral complication, perhaps as the result of secondary pancytopenia associated with drug-induced myelosuppression. Symptoms of myelosuppression may include gingival hemorrhage and increased susceptibility to infections. This condition may profoundly affect decisions regarding oral hygiene procedures and periodontal therapy.

**Treatment considerations**

**Kidney transplantation**

Currently, there are no firm protocols for the dental management of individuals with chronic or end-stage renal disease or for the recipients of renal transplants. A study on 45 renal dialysis patients showed that all had periodontal disease. This means that there is a very high incidence of oral infection in dialysis or transplant patients. Oral infections, including periodontal diseases, may place the patient with renal disease at risk and appropriate measures should be taken to eliminate or to decrease this risk.
Patients with end-stage renal disease have an increased tendency to bleed because of alterations in platelet aggregation and adhesiveness, and this may manifest as petechiae or purpura. Patients undergoing dialysis may be receiving heparin to facilitate blood flow and elimination of toxic waste products and may also be on warfarin supplements to avoid related complications because this may compound the bleeding problem. They also tend to exhibit hypertension due to salt and water retention. Heparin administration and the periodic elimination of toxic waste products may significantly influence the timing of invasive dental procedures, including periodontal therapy. It is usually recommended that periodontal treatment be performed the day after hemodialysis to minimize the risk for systemic infection, although postoperative hemorrhage may be caused by residual heparin accumulation. Caution must be exercised when dealing with patients receiving dialysis. If these individuals have an anastomosis site in an arm, care must be taken to avoid trauma to the area, and the portal should not be used to administer intravenous drugs. In addition, blood pressure measurements and injection of intravenous or intramuscular drugs are contraindicated in that arm.

Patients with chronic renal failure are pre-exposed to hyperkalemia and ensuing cardiac arrhythmias; However, these conditions are not major concerns for short dental procedures that are not highly invasive. Anemia and osteodystrophy are some other concerns of chronic renal failure. Patients on long-term steroids should be questioned and assessed for symptoms such as buffalo hump and moon facies. Steroid supplements can be planned prior to treatment, if deemed necessary, to avoid adrenal crisis. Adrenal crisis can also be avoided by using a stress-reduction protocol. This involves morning appointments, a calm atmosphere, use of conscious sedation, and avoiding any sudden movements during treatment. In the event of an adrenal crisis, the dentist must be prepared to administer an intravenous infusion of a corticosteroid supplement.

The time period after transplantation can be divided into immediate, stable, and chronic rejection. The best time for treatment is the stable period, which is about 6 months after the transplantation. Before proceeding with the treatment, the physician should be consulted for the patient’s immunosuppression level, dialysis schedule, and prophylactic antibiotics. In most cases, the American Heart Association’s regimen for the prevention of bacterial endocarditis is recommended. Most of these patients are psychologically affected and may therefore not show the motivation for proper oral hygiene; the use of antimicrobial mouth rinses can then be considered. Dental or periodontal therapy should be conservative and noninvasive when possible, especially for the first 3 months after transplantation.
Care should be taken in prescribing medications that are metabolized in the kidney because the drugs will be retained in the bloodstream for prolonged periods and may reach toxic levels. These drugs include analgesic agents, such as aspirin, and most nonsteroidal anti-inflammatory drugs. Acetaminophen, codeine, and local anesthetics are metabolized in the liver and, therefore, are safe to use. Some antibiotics, such as aminoglycosides, tetracyclines, and polypeptides (bacitracin and polymyxin), are potentially nephrotoxic, and potassium penicillin should be avoided to avoid excessively high serum potassium salt levels. Conversely, other forms of penicillin are well tolerated. As renal function is reduced, the plasma levels of some of the drugs may be high or prolonged. Nonsteroidal anti-inflammatory drugs and antibiotics, such as erythromycin and clarithromycin, interfere with the action of cyclosporine and could raise its serum levels, rendering the patient more immunosuppressed than desired.

Liver transplantation

Drugs commonly used in dentistry that are metabolized primarily in the liver are as follows: (i) local anesthetics (lidocaine, prilocaine, mepivacaine, and bupivacaine) (ii) analgesics (acetaminophen, ibuprofen, aspirin, meperidine, and codeine) (iii) antibiotics (ampicillin, tetracycline, metronidazole, and vancomycin) and (iv) a sedative (diazepam). Local anesthetics can be used safely when the total dose of 7 mg/kg is not exceeded and when combined with epinephrine. Paracetamol should not be used on a chronic basis (no more than two weeks) and must not exceed a dose of 4 g daily. Ibuprofen and aspirin should be avoided because they have a significant hepatic metabolism. It is preferable to use morphine as a narcotic analgesic rather than meperidine and codeine because morphine has extra-hepatic metabolism. Beta-lactam antibiotics can be used instead of those metabolized in the liver. Sedatives (diazepam, lorazepam, and midazolam) can be used safely if we reduce the dose and if we increase dosing intervals between medications. To date, there is no definite guideline for the dosage adjustment to use these drugs. The decision is made by the treating dentist in consultation with the treating physician who can make recommendations according to the stage of the patient’s disease.

Spontaneous gingival bleeding occurs in end-stage hepatic disease patients as a result of their abnormal bleeding tendencies. Alcoholic cirrhosis patients may show nutritional deficiencies, seen as glossitis, angular cheilitis, mucosal ecchymoses, and petechiae, along with the presence of premalignant lesions. Bilateral parotid enlargement might also be present. Since most coagulation factors are synthesized in the liver, significant liver damage can affect the coagulation phase. Other factors that might contribute to abnormal bleeding tendencies are deficiency of vitamin K,
altered synthesis of clotting factors, and thrombocytopenia seen in chronic liver disease. Hence, one of the main treatment considerations for end-stage liver disease patients is the bleeding tendency. For patients with ascites, the risk of bacterial peritonitis is greater during dental treatment and hence prophylactic antibiotics should be used. Most cases are referrals from the transplant physician and so laboratory results might be available. If laboratory test results are not available, the dentist can order a test. The laboratory test request should include complete blood count with differential, prothrombin time, platelet count, serum aspartate aminotransferase level and serum alanine aminotransferase level. In the event of an invasive procedure, the precautionary measures for hemostasis can include local hemostatic agents, fresh-frozen plasma, vitamin K, platelets, and antifibrinolytic agents at the recommendation of the physician.

For the post-transplant patient, the treatment considerations should include the level of immunosuppression. Dental treatment is recommended in the stable period after the transplant when the patient does not show any signs of rejection or other significant complications. Prophylactic antibiotics, as recommended by the American Heart Association for bacterial endocarditis, should be administered. A laboratory test assessing liver function is best recommended before planning elective dental treatment. Drugs metabolized by the liver should be used with caution and after consultation with the transplant physician.

Heart, lung, and heart–lung transplant patients

The dental management of heart, lung, and heart–lung transplant patients is similar to that of other transplant patients, with the main aim being the reduction of dental infection in the heart–lung and individual organ transplant patient. A positive correlation has been reported between periodontitis and risk for myocardial infarction. Pretransplant management should be based on the presenting condition of the patient after discussion with the physician. The discussion should include the nature and duration of the treatment, along with the drugs to be used during and after treatment. Patients scheduled for lung transplant are usually on oxygen therapy. As a part of dental management, the use of any combustible products should be avoided. Narcotic analgesics should not be considered because of their respiratory-depressant properties. Patients awaiting cardiac transplantation generally have a very low cardiovascular reserve, and hence, the most elective treatments are better performed after the transplant. When planning a pretransplant treatment, the patient’s existing cardiovascular reserve should be taken into consideration. This is necessary to plan the duration of treatment, the posture of the patient during treatment, and drugs
administered before or after treatment. These patients are highly susceptible to hemorrhage due to neutropenia, anemia, and thrombocytopenia. In many cases, the patients can be treated with anticoagulants or antiplatelet drugs. A complete blood count is recommended, including the International Normalized Ratio (INR), and the appropriate hemostatic measures, such as the use of hemostatic agents, should be taken. Anesthesia is recommended without vasoconstrictor because these patients may be more sensitive to epinephrine.

Post-transplant management should account for the risk of infection caused by immunosuppression. It is known that immunosuppression alters bone marrow function, rendering these patients highly susceptible to hemorrhage as a result of neutropenia, anemia, and thrombocytopenia. Prophylactic antibiotic therapy should be considered during dental treatment rendered in the first 6 months after transplantation. After the first 6 months, if the patient reaches an acceptable level of cardiac function and his immunosuppression is at a lower level, antibiotics may not be required.

**Hematopoietic cell transplantation**

BMT is used for individuals with hematologic malignancies or conditions that are unresponsive to chemotherapy or radiation alone. It is often the treatment of choice for leukemia, lymphoma, multiple myeloma, neuroblastoma, some solid tumors, several types of anemia, and other conditions. When marrow suppression is severe, NUG and necrotizing stomatitis are probably best treated with an antibiotics, such as metronidazole. During the early recovery phase, gentle debridement, removal of necrotic bone, use of chlorhexidine mouth rinses, antibiotics, and frequent recall intervals should be employed after consultation with the patient’s oncologist. Brushing and flossing should be generally suspended until white blood cell and/or platelet counts decrease to less than the minimally acceptable levels (1500 absolute neutrophils/mm$^3$ or 20,000 platelets/mm$^3$). At this point, cotton swabs, gauze sponges, soft sponge sticks, and chlorhexidine rinses are appropriate for oral cleansing until sufficient recovery of marrow cells has been achieved. These patients are then managed similar to individuals receiving chemoradiation therapy. The screening laboratory tests for the pre-transplant patient should include a complete blood count, a white blood cell count, a platelet count, and determination of the hemoglobin and hematocrit levels. Prophylactic antibiotics must be used if the patient has neutropenia, and elective treatment should be performed when the patient does not have any acute complications. It is important to measure the patient’s bleeding time on the day when scaling, extractions, or any procedure that might induce bleeding, are to be carried out. If the patient’s bleeding time is prolonged, treatment should be delayed and
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the patient referred back to the physician. Treatment can then be scheduled for when the bleeding time is within the normal range. Oral GVHD can usually be controlled using topical and/or systemic corticosteroids and other immunosuppressant drugs and by maintenance of meticulous oral hygiene coupled with frequent dental visits.13

The dental management of mucositis is usually palliative in nature. Rinsing with lukewarm saline or sodium bicarbonate (5%) in water may be of some benefit, and use of a soothing mixture of kaolin and diphenhydramine (Benadryl) is sometimes recommended. However, a systematic review of the literature indicated that most topical agents are of little benefit in reducing the discomfort from mucositis. Only allopurinol mouthwash and vitamin E were reported to be slightly beneficial in a review of randomized controlled studies.28 Topical anesthetic agents, such as lidocaine hydrochloride, may partially reduce discomfort. Patients should be advised to avoid use of irritating substances such as alcohol, tobacco products, or spicy foods.

Pancreas transplantation

The dental management of patients undergoing pancreas transplantation should address the patient’s ability to metabolize glucose. These patients usually have significant glucose-management problems, and hence, their glucose levels should be evaluated before treatment. These patients can be brittle insulin-dependent diabetics, which implies that they can experience sharp alterations in their glucose levels. Hence, they are prone to ketoacidosis and insulin shock. Post-transplant management of these patients is similar to that of the kidney transplant patients, with special focus on the patient’s glucose levels.

Conclusions

The need for the dental evaluation of transplant patients before and after transplantation is increasing with the rise in the number of transplants being performed. It is important to co-ordinate all dental treatments with the physician because the health of the patients can deteriorate during or after the dental treatment. As with all patients, achieving excellent oral hygiene may be difficult, but it should be emphasized that oral infections can increase the chances of systemic infections as a result of immunosuppression. Hence, it is important that the dental practitioner have a strong knowledge base of medicine to be capable of effectively managing organ transplant patients.

References


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