

Periodontal treatment considerations for cell transplant and organ transplant patients

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Organ replacement has been prevalent in the mythology of medicine and surgery for several hundred years. An Indian legend from the 12th century BC recounts the powers of the Hindu god, Shiva, who transplanted the head of an elephant to his child, Lord Ganesha, the god of wisdom and health (84). One of the major medical and scientific accomplishments in the latter half of the 20th century was the replacement of failing kidneys, livers, hearts or lungs through transplantation with a healthy organ (68). Over the last 30 years, this treatment modality has changed from being a last-ditch desperate effort to prolong life to being an option for treating and managing a variety of diseases and conditions (120). The improved prognosis following organ transplant is a result of superior methods of obtaining donor-patient tissue matches, proper methods of transportation, understanding the immune system, and the discovery of potent immunosuppressive drugs that could delay or prevent the rejection of the transplanted organs (63).

Although transplantation is beneficial, it is not without a range of complications, beginning with life-threatening infections and ending with graft rejection. All transplant patients are typically screened for adequate dental health before an elective organ transplant to eliminate or treat active sites of infection in the oral cavity (136). In all of these cases, careful dental protocols must be observed to provide safe and effective care for patients. There are several organs that it is currently possible to transplant. The most common of these are the kidney, liver, heart, lung and pancreas. The major limiting factor in organ transplantation is the availability of organs for transplant. In the U.S.A., data on patients waiting for transplants, organs donated, transplants performed and clinical outcomes has been maintained by the United Network for Organ Sharing. Since 1987, the

United Network for Organ Sharing has compiled data on more than 300,000 transplant patients. According to the United Network for Organ Sharing, as of December 30th 2005, the waiting list for solid organ transplants was 97,117 and only approximately 25,000 organ transplants had been performed each year in the previous 2 years (148). Recently, an analysis on the life years that could be saved by a deceased organ donor was carried out and, based on the projected survival of the organ transplant recipients, it was estimated that an average of 30.8 additional years could be distributed over 2.9 organs transplanted successfully. It was also estimated that an additional 55.8 life years could be added from a single donor if all six organs were transplanted to different recipients successfully (132). There seems to be no racial disparity among African-Americans and Caucasians for successful outcomes in transplantation when compared for functional performance and quality of life (106). This article will briefly discuss the conditions leading to organ failure and the medical concerns in treating the end-stage organ failure patient. The immunobiology, pharmacology, oral considerations and dental management of the organ transplant recipient will be discussed in the following sections.

Hematopoietic cell transplantation

Hematopoietic cell transplantation (also called bone marrow transplantation) is the transplantation of hematopoietic stem cells. Hematopoietic cell transplantation has become the preferred term because the cells can be obtained from peripheral and umbilical cord blood, and not just the bone marrow. This procedure is used to replace an abnormal, nonmalignant lymphohematopoietic cell with a

normal one from the donor, and to allow the use of higher-dose myelosuppressive therapy. This modality has become a viable option of treatment, not just because of the effectiveness of the treatment, but also as a result of the increased availability of donors (2).

Hematopoietic cell transplantation is used to treat a group of both malignant and nonmalignant conditions. The malignant conditions include acute leukemia, chronic leukemia, myelodysplasia, lymphoma, myeloma and some solid tumors with metastasis. The nonmalignant conditions include aplastic anemia, hemoglobinopathies and any congenital conditions with abnormalities in the lymphohematopoietic system (4, 13, 97). The number of diseases for which hematopoietic cell transplantation may be used as a treatment option is increasing because of advances in science and understanding of the disease. Currently, hematopoietic cell transplantation is the predominant treatment modality for malignant conditions, particularly leukemia.

Two kinds of transplantations are possible: (i) allogeneic transplantation, which involves a donor and recipient who are not immunologically identical (histocompatible); and (ii) autologous transplantation, which is the removal and storage of the patient's own stem cells that will be re-infused after myeloablative therapy (152). With allogeneic transplantation, there is an increased risk of graft-vs.-host disease, which does not occur with the autologous transplant. However, the autologous stem cells may have contaminated tumor cells that could lead to a relapse, and therefore proper screening needs to be carried out to avoid such an occurrence. Hematopoietic stem cells are sourced from the bone marrow and the peripheral blood progenitor cells. Both sources have been used with variable success rates without much statistical significance, as far as transplant-free mortality and leukemia-free survival are concerned (2).

Transplantation with peripheral blood progenitor cells offers the advantage of a faster neutrophil and platelet recovery (73). This procedure is performed with bone marrow from the iliac crest. Typically, $1.5-5 \times 10^8$ nucleated marrow cells per kg are obtained for an allogeneic transplantation procedure. Umbilical cord blood has recently been considered for transplantation because it contains a low number of T cells and hence may reduce the graft-vs.-host reaction. One of the drawbacks of cord blood is that it is usually slow in engraftment. The peripheral blood cells reach their lowest level within 1 week of the transplant owing to the presurgical preparative phase of treatment. After 1 week, the inducted stem

cells start to be seen in the peripheral blood. The time frame for this to occur depends mainly on the source of stem cells, along with pre-grafting prophylaxis and the use of different growth factors during treatment.

Graft-vs.-host disease

Graft-vs.-host disease usually results from allogeneic T cells reacting with the antigenic host cells. The allogeneic T cells could be part of the inoculum that was transferred with grafted cells or may have developed from the stem cells to react with the host targets. A 3-month window separates chronic graft-vs.-host disease from the acute graft-vs.-host disease, with the acute episode occurring within the first 3 months of transplantation and chronic graft-vs.-host disease occurring after that time period. Acute graft-vs.-host disease usually occurs within the first 2-4 weeks of grafting. Hematopoietic stem cell transplant recipients generally develop a maculopapular rash, with diarrhea and persistent anorexia. The liver enzymes and functions are altered, with increased serum levels of bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine being present. As many conditions can have the same clinical and laboratory presentation, it is recommended that the diagnosis be carried out with a clinical evaluation of the skin, laboratory analysis of liver function and a bone marrow biopsy. The histopathology of acute graft-vs.-host disease will usually show endothelial damage with lymphocytic infiltration.

Chronic graft-vs.-host disease does not have a time limit, but usually starts at any time 3 months after acute graft-vs.-host disease and may progress before symptoms are seen. In such cases, patients may need to be on continuous immunosuppression until symptoms subside.

Infection is a concern during the initial post-transplantation period, and the main causative agents are gram-positive bacteria, fungi (*Aspergillus*) and viruses, such as cytomegalovirus (Table 1). After 3 months of engraftment, the risk of infection diminishes considerably, unless chronic graft-vs.-host disease develops, and the immunosuppression may be continued for prolonged periods of time. In general, most transplant centers recommend a combination of sulfamethoxazole and trimethoprim for patients with immunosuppression, and few centers recommend an acyclovir regimen for 1 year, in order to avoid varicella-zoster viral infection (Table 2).

Table 1. Risk factors for infection in hematopoietic stem cell transplant and organ transplant patients

Recipient	Underlying pathosis, age, colonization by pathogens and lack of specific antibodies, previous therapy and presenting clinical state
Transplantation	Infected graft, surgical factors, postoperative instrumentation, interrupted lymphatic drainage
Immunosuppression	Type of immunosuppressive regimen, immunomodulating viruses

Adapted from Gavalda et al. (61).

Table 2. Host immune system defects in the hematopoietic stem cell transplant patient

Phases	Defects
Phase I (pre-engraftment period <30 days)	Neutropenia, mucositis, acute graft-vs.-host disease
Phase II (post-engraftment period 30–100 days)	Impaired cellular immunity, acute and chronic graft-vs.-host disease
Phase III (late phase, > 100 days)	Impaired cellular and humoral immunity, chronic graft-vs.-host disease

Adapted from Sepkowitz (135).

Prehematopoietic cell transplantation dental evaluation

The main purpose of prehematopoietic cell transplantation dental evaluation is to eliminate any possible infection that may cause significant concern or life-threatening infections during the time of post-transplantation neutropenia (7). Teeth with advanced dental caries and periodontal disease are considered, by the National Institute of Health, as dental foci of systemic infections in the immunocompromised host (108). Some studies conducted on cancer patients have shown that patients with periodontal disease show an increased chance of bacteremia compared with individuals who do not have similar levels of disease (64, 124, 128). Microorganisms, including *Capsocytophaga* species, *Fusobacterium nucleatum* and many others, have been associated with septicemia and other post-transplant infections. Most notably, viridans streptococci have been identified

with increasing frequency in septicemias seen in neutropenic cancer patients (15). Although these bacteria have been implicated, there has been evidence of a shift in the bacterial population of the subgingival region after prophylactic antibiotic administration in the period immediately after the transplant (128). A routine full-mouth survey and panoramic X-rays are recommended. The full-mouth X-rays provide adequate information to identify and treat caries, periodontal disease and defective restorations. Panoramic X-rays provide information on impacted teeth, neoplasms and multiple myeloma, especially in patients needing hematopoietic cell transplantation (14). Appropriate diagnosis of the periodontal status will guide early and prompt treatment, and thereby facilitate early hematopoietic stem cell transplantation (97). The patient often presents for dental treatment just a few weeks before transplant surgery and therefore offers limited time to complete all of the required treatment. Dental treatments aimed at reducing infection include scaling and root planing followed by restorations and extractions (47). When patients are undergoing radiation and chemotherapy, brushing and flossing are discontinued for the immediate postoperative period and resumed only after the white blood cell counts start an upward trend. During this period, the oral hygiene practices recommended include the use of chlorhexidine rinses with cotton tips or sponge swabs (26, 98, 130).

Dental management

As with all other transplant patients, it is important to consult the physician before treatment planning the hematopoietic cell transplantation patient. 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. Treatment should be aimed at reducing oral infection (131). 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 (118). It is important to know the patient's bleeding time on the day when scaling, extractions, or any procedure that might induce bleeding, are to be carried out (107). If the patient's bleeding time is prolonged, treatment should be delayed and patient referred back to their physician. Treatment can then be scheduled for when the bleeding time is within the normal range.

Kidney transplantation

Kidney transplantation is carried out to replace a failed kidney caused by acute or chronic disease. In the U.S.A., it is estimated that 5% of hospital admissions and 30% of intensive care unit admissions are because of acute renal failure (150). Acute renal failure is defined as an abrupt decrease in renal function occurring within hours to days. This is sufficient to result in the retention of nitrogenous waste, as measured by elevations in blood urea nitrogen and creatinine levels. However, it is very unlikely for acute renal failure to be seen in an outpatient dental setting. Therefore, the remainder of this discussion will be focused on chronic renal failure and end-stage renal disease. Chronic renal failure is defined as a persistent impairment of kidney function occurring over a few months or years. Clinically, it often involves a progressive loss of kidney function and may result in complete renal failure, necessitating renal replacement therapy (i.e. dialysis or transplantation). When renal replacement therapy is required, the condition is termed end-stage renal disease. Both sexes are affected equally by chronic renal failure, but Native-Americans and African-Americans have a higher incidence than Caucasians. Chronic renal failure occurs predominantly in the elderly population (> 65 years of age) (65). The effective functioning of a kidney is evaluated by measuring the glomerular filtration rate (i.e. the rate at which an ultrafiltrate of plasma is produced by glomeruli per unit of time). It is the best estimate of the number of functioning nephrons or functional renal mass, with the normal glomerular filtration rate being 80–120 ml/min (150).

Chronic renal failure is rarely reversible and may continue, even after the inciting event is treated. Damage to the renal tissues results in a reduction of the renal mass. Upon overload, the remaining tissues undergo hypertrophy, fibrosis and sclerosis. This further reduces renal function, leading to renal failure. Signs and symptoms depend on the degree of renal dysfunction, and the cause and the rate of renal failure. Presenting features of chronic renal failure are often nonspecific and include fatigue, weakness, shortness of breath, anorexia, vomiting, hiccups, irritability and retrosternal pain from pericarditis. Patients experiencing chronic renal failure may have pale skin, with signs of bruising, and their oral odor is characteristically fishy (uremic fetor) (11, 99). They also tend to exhibit confusion and an inability to concentrate. Chronic renal failure is irreversible, and while medical management of the cause is required,

the reduction in renal capacity also has to be addressed. The medical management of the chronic renal failure patient begins with dietary management and is often followed by renal replacement therapy, which involves dialysis and/or kidney transplantation.

Diet

Protein intake, not exceeding 1.0 g/kg/day, has been shown to slow the progression of renal failure. Endogenous protein catabolism is minimized by providing sufficient carbohydrate and fat to meet energy requirements and prevent ketosis. Sodium (salt) and water restriction is also required to maintain balance, along with potassium, phosphorus and magnesium restriction. Because dietary restrictions may reduce the necessary vitamin intake, patients should take a multivitamin preparation containing water-soluble vitamins.

Dialysis

Dialysis is performed in one of two ways: hemodialysis or peritoneal dialysis. During hemodialysis, the patient's blood is heparinized and circulated through a dialysis machine to remove waste products. Hemodialysis is usually performed three times a week, with each session taking approximately 3.5 hours (depending on the patient). Vascular access for hemodialysis is accomplished with an arteriovenous fistula or a venous catheter (11, 27, 28, 150).

An arteriovenous fistula is surgically created by connecting a forearm artery directly into a vein. This allows more blood flow into the vein, which enlarges, thus facilitating the repeated insertions needed for hemodialysis. It takes 6–8 weeks or longer for a fistula to develop after surgery. Once established, an arteriovenous fistula lasts for years, and is less likely than other forms of vascular access to clot or become infected (137). If a venous catheter is used, it is inserted into the subclavian, internal jugular, or (less commonly) femoral vein. It is then advanced towards the heart until it reaches the superior vena cava or right atrium. This is the fastest way to gain vascular access, but is also the most likely to become infected or clotted.

Peritoneal dialysis is most favored by the patients. In this method, the patient's own peritonium acts as the dialysis membrane. A catheter is used to insert the dialysate (cleaning solution) into the peritonium. With peritoneal dialysis, patients can exchange the dialysate themselves about four times a day or have

the machine automatically perform the exchanges at night. The most common complication of peritoneal dialysis is peritonitis.

Drugs that are excreted by the kidneys are eliminated twofold less efficiently when the glomerular filtration rate drops to 50 ml/min, and may reach toxic levels at a lower glomerular filtration rate. Therefore, drug doses may need to be reduced and administration time prolonged. Nonsteroidal anti-inflammatory drugs and aspirin increase platelet dysfunction and should therefore be avoided.

Kidney transplantation

A kidney transplant now represents the treatment of choice for patients with end-stage renal disease (80). It is becoming more common, with older age becoming less of a barrier than it used to be. Compared with dialysis, renal transplantation is associated with better patient survival and superior quality of life, and is more cost-effective. Currently, in the U.S.A., there are close to 65,000 patients awaiting a kidney transplant (148). As a result of the high success rate of the procedure, the waiting list has grown dramatically since the 1990s. However, the number of available organs has not kept pace, resulting in prolonged waiting periods, because most renal transplants are from deceased donors. Immunosuppressive drugs, such as corticosteroids, azathioprine and cyclosporine, are required after the transplantation procedure. Most centers now report patient survival rates exceeding 95% during the first post-transplant year for all kidney recipients. Living-donor transplants still have an advantage over cadaver donor transplants, but even this difference is diminishing with modern day immunosuppression therapies. Patients need to undergo a battery of tests and examinations before a transplant can be performed, and a dental evaluation is just one of many that a patient awaiting renal transplant has to undergo before the actual transplant.

Organ donors

Cadaver donor

These are from fatalities caused by head injury, when there is no known damage to the organs to be transplanted. After the brain is declared dead, the cardiovascular and respiratory functions are artificially maintained until the organs are harvested and transplanted within a 12-hour time period. The

United Network of Organ Sharing is the organization that currently monitors and allocates patients for the transplantation, based on the severity of need. The cadavers should be free of malignancy, neoplastic disease, hepatitis or human immunodeficiency virus for fear of transmission to the recipient.

Living donor

Living donors are usually family members who at least have partial human leukocyte antigen compatibility, which reduces the chances of rejection. It is desirable to have blood group matching between ABO groups, although an O-group donor can donate for A, B and AB groups in rare circumstances. The surgeons prefer laparoscopic surgery for the living donors because of less postoperative pain, fewer complications and less scarring.

The transplant procedure

The standard method involves an extraperitoneal approach. After the native kidney has been removed, the donor kidney is placed in a fairly retroperitoneal, heterotopic position. A heterotopic position is one where the recipient site is anatomically different from the donor site, and an orthotopic position is one where both are anatomically similar. The decision to place the kidney in the left or right iliac fossa is based on the anticipation of a pancreas transplant. If a pancreas transplant is not anticipated, the right iliac fossa is the desired area. The internal iliac artery is then used as the inflow vessel and is anastomosed with the grafted kidney. After the anastomosis is complete and the kidney perfused, urinary continuity is restored (80).

Post-surgical complications

The early complications that occur after surgery include hemorrhage, lymphocele, and vascular and urinary complications. Organ rejection is the major complication, and long-term studies show that chronic rejection is the second most important cause of graft loss (81). Patient death is the leading cause of graft failure and, in most cases, cardiovascular disease is the cause of death in transplant patients (80). The predictor of chronic rejection is a previous episode of acute rejection that occurred within the first year of the transplant surgery. Rejection rarely occurs, but when it does, it presents with swelling and tenderness over the allograft, with accompanying fever. When chronic rejection is suspected, a biopsy is recommended to make a diagnosis and a rise in

serum creatinine is seen during rejection. Infection from viruses, particularly cytomegalovirus, is common and is typically seen after the first month. Infections from other viruses, fungi, bacteria and parasites may also be seen in the post-transplant period as a result of the immunosuppression. Hypertension is the most common complication seen in more than 80% of transplanted patients (31). The risk of malignancy and diabetes mellitus is quite high in this group of patients.

Dental management

Currently, there are no firm protocols for the dental management of transplant patients (69). A recent study showed 100% periodontal disease in a group of 45 renal dialysis patients. This means that there is a very high incidence of oral infection in dialysis or transplant patients (110). Management of chronic renal failure or end-stage renal disease patients should be performed in co-ordination with the treating physician (39, 40). It is recommended that all foci of infection be removed prior to the transplant procedure (25, 111, 142). Dental treatment planning can begin with a full-mouth series of radiographs. The infection control protocol may involve extraction of teeth with poor or hopeless prognosis, scaling and root planing, restoration of carious lesions and endodontic treatment where needed (23). Before proceeding with 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 prevention of bacterial endocarditis is recommended (33, 34). Most of these patients are psychologically affected and hence may not show the motivation for proper oral hygiene – the use of antimicrobial mouthrinses can therefore be considered. The use of chlorhexidine has shown good reduction in plaque levels for this group of patients (130). Some of the main concerns with the treatment of the end-stage renal disease patients is the drug metabolism of some of the drugs used in dentistry (125). As renal function is reduced, the plasma levels of some of the drugs may be high or prolonged. Aspirin and non-steroidal anti-inflammatory drugs should be avoided as much as possible because of their effect on bleeding. Acetaminophen and codeine can be given for post-operative pain management. Aminoglycosides, tetracyclines and polypeptide antibiotics should be avoided because they are nephrotoxic. Local anesthetics are metabolized in the liver and hence are safe to use for dental procedures.

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 (55, 125). Patients undergoing dialysis may be receiving heparin to prevent clotting during dialysis and may also be on warfarin supplements to avoid related complications because this may compound the bleeding problem (23). They also tend to exhibit hypertension, from salt and water retention (89). Patients with chronic renal failure are pre-exposed to hyperkalemia and ensuing cardiac arrhythmias. It is not a major concern 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 an episode of adrenal crisis. Avoiding an adrenal crisis is also accomplished 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 give an intravenous infusion of a corticosteroid supplement (46, 111).

The time period after transplantation can be divided into immediate, stable and chronic rejection (6). The best time for treatment is during the stable period, which is about 6 months after the transplantation. It is the period when the graft does not show any signs of rejection. The risk of infection, as a result of immunosuppression, is high, along with the chance of rejection. Hence, dental treatment should be planned after careful discussion with the physician. There is usually a recommendation for prophylactic antibiotics, although there is no evidence-based research for this. Nonsteroidal anti-inflammatory drugs, and antibiotics such as erythromycin and clarithromycin, interfere with cyclosporine and could raise the serum levels, rendering the patient more immunosuppressed than desired (68).

Pancreas transplantation

Pancreas transplantation can be carried out in conjunction with kidney transplantation, after kidney transplantation, or as a pancreas transplant alone. Patients who undergo the simultaneous procedure are those with type I diabetes and end-stage renal disease with adequate cardiac reserve to undergo the

procedure simultaneously. Patients who undergo pancreas transplantation after kidney transplantation are those who have developed or continue to have type I diabetes after obtaining a stable kidney graft and who want to have it corrected. The success rate of the pancreatic graft is improved when it is performed with, or after, kidney transplantation, than when it is performed alone. The indication for pancreas transplantation alone is in cases of frequently severe hypoglycemic events (16). The simultaneous kidney and pancreas transplant is the most common type of pancreas transplant carried out (10). The combination transplant, as analyzed by one study, represented almost 78% of pancreas transplants carried out, and transplantation of the pancreas alone was generally less than 5% (66, 96).

The main concern with pancreas transplantation, as with all other transplants, is the long-term immunosuppression. On comparing the need to have a pancreas transplant with lifelong immunosuppression to avoid exogenous insulin, it is generally not recommended unless the patient has severe diabetic complications. Hence, pancreas transplantation is mainly undertaken in diabetic patients with kidney failure as an adjunctive procedure because these patients would be on immunosuppressants for life and it relieves the patient of exogenous insulin and other diabetic complications. The main contra-indications for pancreas transplantation are malignancy and infection. The donor, in most cases, is brain dead and very rarely can a hemisected pancreas be utilized from a live donor.

One recent approach, carried out with limited success, is isolation of the islet cells that need to be transplanted, leaving behind the complicated exocrine portion (91). This makes way for an outpatient procedure of injecting the islet cells through the portal vein. The cells then engraft in the hepatic parenchyma and secrete insulin.

The complications encountered after pancreas transplant surgery are hemorrhage, thrombosis, pancreatitis and rejection. An episode of rejection is also identified by increases in serum creatinine, amylase and glucose levels. Long-term complications include recurrent diabetes, macrovascular disease, infection and risk of cancer. A regular examination for diabetes-associated complications should be carried out periodically. The success rate of pancreas transplants is relatively lower compared with those of other organs, simply because the pancreas has an exocrine component that is not highly vascular.

The dental management of the patient who needs a pancreas transplant should include the

patient's ability to metabolize glucose. These patients usually have significant glucose-management problems and hence their glucose levels should be considered before treatment. These patients can be brittle insulin-dependent diabetics, meaning that they can experience sharp alterations in their glucose levels. Hence, they are prone to ketoacidosis and insulin shock. Post-transplant management is similar to that of the kidney transplant patient, with specific attention paid to the patient's glucose levels.

Liver transplantation

In the U.S.A., end-stage liver disease accounts for more than 25,000 deaths a year. Over the past decade, liver transplantation has become an effective, and often life-saving, intervention for end-stage liver disease patients. Liver transplantation is a relatively new therapy, with most liver transplants being performed in the past 15 years. As much as 30% of the liver transplant literature has been published from 1997 to date. Recently, liver transplantation has been used as a treatment modality for patients with a variety of diseases and conditions, including primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia, cystic fibrosis, hemochromatosis, alpha-1-antitrypsin disease, Laennec's (alcohol-related) cirrhosis, hepatitis B and C cirrhosis, cryptogenic cirrhosis, hepatocellular carcinoma and fulminant hepatic failure. Transplantation is also a treatment option for rare liver diseases, such as Budd-Chiari syndrome, Wilson's disease, certain cystic diseases of the liver and other miscellaneous diseases (87).

Contraindications for liver transplant are constantly changing and can vary with the transplant centers undertaking the procedure. The contraindications for liver transplant have been considerably reduced in the past 15 years, with the advancement of science and supportive data. The widely accepted contraindications include uncontrolled infection, human immunodeficiency virus seropositivity, extrahepatic malignancy, advanced hepatic malignancy, active substance abuse, medical noncompliance and irreversible brain damage. Relative contraindications are extreme age groups, anatomical difficulties, severe extrahepatic diseases and adverse psychosocial factors.

The assessment of liver injury or damage is carried out by the physician, taking the clinical presentation and laboratory findings into consideration.

The clinical presentation of the hepatitis patients usually has a prodromal phase of abdominal pain, anorexia, nausea and vomiting. This is followed by the icteric phase, characterized by jaundice, which is the brownish–yellow discoloration of the skin, eyes, mucous membranes of the oral cavity and urine. Patients also present with hepatomegaly and splenomegaly. The recovery phase is characterized by the disappearance of these presenting features.

Hepatitis C viral infection is the currently the most common indication for liver transplantation in the U.S.A.. One of the major concerns with hepatitis C patients is that in almost all of the cases the graft becomes re-infected with the hepatitis C virus. This has also been the case with the hepatitis B virus, but has been overcome in patients with fulminant hepatic failure because they develop a strong immune response against the hepatitis B virus. As with alcohol-related liver disease patients, the main concern has been the recidivistic tendency of these patients. The controversy that surrounds transplants in patients who develop cirrhosis because of alcohol abuse is an ethical issue. In the U.S.A., the state of Oregon considers nonalcohol-related cirrhosis twice more than alcohol-related cirrhosis in the order for receiving liver transplants (42).

Chronic hepatitis could be asymptomatic for a variable period of time, from a few years to a few decades. Some of the early symptoms, mentioned above, can present in an irregular manner, based on the extent of damage to the organ. The destructive process is a combination of the action of the virus and the secondary changes that the liver undergoes because of the inflammation. Chronic hepatitis can lead to end-stage liver disease in the form of cirrhosis, which will show hepatic firmness, hepatomegaly, splenomegaly and diffuse liver failure. Diffuse liver failure is seen as bleeding esophageal varices, spider angiomas, ascites and jaundice. Cirrhosis is diagnosed with a biopsy, which shows extensive fibrosis and regenerative nodules in the liver parenchyma. The laboratory findings that are used as determinants of hepatitis and its severity are the transaminases, namely aspartate aminotransferase and alanine aminotransferase. An elevation of these enzyme levels is an indication of altered hepatic function. Alkaline phosphatase and bilirubin are other enzymes that show altered levels. Cirrhosis and end-stage liver disease show hypoalbuminemia and prolonged prothrombin time, and higher aspartate aminotransferase levels compared with alanine aminotransferase levels (41).

Organ donors

Cadaver donor

The United Network for Organ Sharing currently utilizes the Model for End-stage Liver Disease to make a decision on liver allocation. This model is based on three factors: (i) serum creatinine; (ii) bilirubin; and (iii) INR (International Normalized Ratio). These three factors give an assessment of the severity of the disease. In the case of pediatric patients, albumin replaces creatinine, with age and growth failure being taken into consideration.

Living donors

Living donor transplantation is currently gaining popularity, especially for pediatric recipients. The liver, which comprises two lobes, can be split, and the left lobe donated. The advantage of the living donor is that the procedure can be planned well because it is not an emergency. It can also be life saving, in extreme cases, as the recipient does not need to wait for a brain-dead donor. The drawbacks are for the donor, as they may become debilitated for a reasonable period of time and may face complications because of the donation and the surgical procedure.

Liver transplant procedure

The liver transplant procedure involves three steps. The first step is the dissection of the recipient's liver, followed by the second step, in which the major vessels of the liver (such as the hepatic artery and portal vein) are interrupted of their blood flow to the area. After this stage, the donor liver is revascularized and the third step involves reperfusion, in which the donor liver is implanted in the recipient. After these three major steps are accomplished, anastomoses of the smaller vessels is performed to complete the procedure (116). The surgery can last from 6–18 hours, and recipients generally require blood transfusions, during surgery, as a result of the amount of blood loss (80).

The average patient spends, in general, 5–10 days in hospital after the transplant procedure. During this time, the patient is usually on intravenous or intramuscular medications and as the bowel functions resume, medications are switched to the oral route and the diet is advanced, as tolerated. The survival rates following liver transplantation have improved dramatically, with most centers reporting survival rates of >90% in the first year.

Post-transplant complications

Despite the recent advances in immunosuppressant medications, 40–60% of patients experience at least one episode of acute cellular rejection in the first year of transplantation. Rejection can be acute or chronic, based on the type of destruction experienced by the transplanted liver (94). Acute rejection usually occurs within the first year post-surgery. The signs and symptoms of acute rejection are jaundice, low-grade fever, malaise, loss of appetite and upper right abdominal pain, although these symptoms are not always present. The laboratory findings show abnormal elevation of aspartate aminotransferase and alanine aminotransferase levels, along with alkaline phosphatase, bilirubin, prothrombin time and ammonia. The mechanism of acute rejection is primarily mediated by T lymphocytes. Apart from their cytotoxic effect on the liver cells, they also serve as enhancers for macrophages and eosinophils in the pathogenesis of rejection, although the mechanism of this is not known. The diagnosis of acute rejection can be made only with biopsy. The histopathological picture of acute rejection shows cellular inflammatory infiltrate along the epithelium of the bile ducts and the endothelium of the portal and hepatic veins.

Chronic rejection occurs, in general, 1 year after the transplant and, in most cases, is asymptomatic, although a combination of any of the above-mentioned clinical signs and symptoms may develop. Initial signs can be seen as elevated levels of alkaline phosphatase, γ -glutamyl transpeptidase and bilirubin that do not improve with steroid therapy. As with acute rejection, diagnosis of chronic rejection is also made with biopsy. The histopathological picture shows a significant loss in bile ducts, and an additional finding may be the macrophage invasion of the muscular portion of the arteries at the intima and subintima levels. Chronic rejection is also called the vanishing bile duct syndrome (94).

One of the rare complications is progressive multifocal leukoencephalopathy, which is a neural demyelination infection caused by JC virus. It is usually fatal within a few months (29, 138).

Dental management

The aim of dental treatment for the pretransplant patient is to try and eliminate or reduce the oral foci of infection, which might be a threat to the success of a liver transplantation procedure. The aim of treating oral infection is to reduce or eliminate the chance of developing systemic infections of oral origin. Drugs

commonly used in dentistry that are metabolized primarily in the liver are: (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) (125). To date, there is no definite guideline for the dosage adjustment to use these drugs. The decision is made by the treating dentist after consulting the treating physician, who will make recommendations based on 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 (59, 152). As 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 (125). 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. In the instance of laboratory results not being available, the dentist can order one. The laboratory order request should include complete blood count with differential, prothrombin time, platelet count, aspartate aminotransferase and alanine aminotransferase. 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 (77). Dental treatment is recommended in the stable period after the transplant when the patient does not show any signs of rejection or significant other complications. Prophylactic antibiotics, as recommended by the American Heart Association for bacterial endocarditis, should be given (62, 103). 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 with the recommendation of the transplant physician.

Heart transplantation

In the United States, 60,000 people under the age of 65 die as a result of end-stage heart disease (38). The New York Heart Association has a functional classification for patients with heart failure and divides them into classes I–IV. Patients who are candidates for transplantation fall into classes III or IV. The class III patients have severe limitation in physical activity but are comfortable at rest, and class IV patients have symptoms at rest, which can become aggravated during rest (88). The main causes of end-stage heart disease are idiopathic cardiomyopathy and end-stage coronary artery disease. Since the first clinically successful cardiac transplant was performed in 1967, several thousand heart transplants have been performed in all age groups, from newborns to 60-year-old patients. Currently, cadavers are only used for heart transplants.

As donor hearts are hard to find, tissue matching is not always performed. ABO blood type matching, negative lymphocyte cross matching, heart size and cytomegalovirus seronegativity are evaluated before transplantation (8, 134).

The primary indication for heart transplantation is end-stage heart failure. This can be the result of ischemic cardiomyopathy with intractable angina. The other conditions that preclude transplantation are recurrent ventricular arrhythmias, coronary artery disease, and valvular and congenital heart disease (19).

The contra-indications for heart transplant are like those for any other organ transplant, where the patient should not have any active malignancies or infection and should not have other debilitating conditions that would affect the long-term survival of the individual. One other major contra-indication is irreversible pulmonary hypertension, which could cause right heart failure after transplantation (126). Some other general contraindications include patient noncompliance and lack of psychosocial support to go through the entire treatment.

Patients with end-stage heart failure are usually on a group of medications, which typically may include most or all of the following: digoxin, an angiotensin-converting enzyme inhibitor, a loop diuretic, thiazide diuretics, long-acting nitrates, vasodilators and anti-coagulants. Some patients may be on ventricular assist devices which act as bridges to transplantation.

These are devices that are inserted prior to surgery to help with maintaining the ventricular function (153). It has also been shown that patients who have these devices show improved return of function after the transplantation (22).

Surgical technique

The surgical technique involves two different teams performing the donor and recipient procedures. The donor harvesting team surgically removes the heart after arresting it with cold crystalloid at major vessels in an anatomical method at specified points. The organ is then cooled and transported in a physiological salt solution to the other surgical team at a different room or hospital. The time limit recommended for placement is 2–3 hours. The recipient team, meanwhile, has the diseased heart removed and the area ready for transplantation. The transplanted heart is then positioned anatomically, and anastomoses of the major and minor vessels is carried out (80).

Post-transplant complications

As with other solid organs, the major complication is organ rejection. Acute rejection is of three types: (i) hyperacute; (ii) acute cellular; and (iii) acute vascular. Hyperacute rejection occurs within minutes to hours of the surgery. Acute cellular rejection can occur within 3 weeks of the procedure. Acute vascular (humoral) rejection occurs within the first 6 weeks (134). The disorders are categorized based on the type of immune response that are manifested in the transplanted heart. Chronic rejection occurs as atherosclerosis of the heart. It is believed to occur as an injury to the endothelial lining of the coronary arteries, with development of intimal hypertrophy. Infection of the graft with virus, bacteria, fungi and parasites is another complication that can occur after the transplant procedure. Although the patients are usually on a prophylactic regimen, infections occur and may sometimes be life threatening. Post-transplantation malignancy has been associated with chronic immunosuppression (139). The incidence of lymphoproliferative disorders is somewhat higher for heart transplant patients, at 1.8%, whereas kidney transplant patients have a lower incidence rate, at 1%. Liver transplant patients have a higher incidence of lymphoproliferative disorders, at almost 3%. For some reason, the heart–lung combined transplants tend to show the highest rate of malignancies, at 4.6% (121). There has been reasonable evidence to

show that Epstein–Barr virus infections are related to the incidence of the lymphoproliferative disorder in these patients (70, 71, 154). Allograft vasculopathy, an obliterative coronary artery disease, is a complication that occurs in 10% of the transplant patients in the first year, and in 50% at 5 years, post-transplantation (60, 149).

Lung transplantation

Lung transplantation is becoming a recommended treatment for patients with nonmalignant end-stage lung disease. There has been a significant increase in the number of lung transplants carried out in the past decade, with 1,400–1,500 being performed every year.

Isolated lung transplants are performed (individually, as one at a time, or two in some cases) for a number of conditions. Combined heart and lung transplants are performed in specific conditions. Chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis generally have single lung transplants, based on the extent of involvement (24, 44, 45). Cystic fibrosis and pulmonary hypertension are two conditions where two individual lung transplants are performed, especially in pulmonary hypertension in the absence of right side heart failure (147).

The complications associated with the lung transplantation are graft dysfunction, which typically occurs within the first week, as a result of ischemia and airway obstruction. Acute rejection might occur within the first year and presents with hypoxemia, dyspnea, inspiratory crackles, low-grade fever and declining lung function. Chronic rejection is similar in presentation to bronchiolitis obliterans syndrome, which is characterized by continued decrease in forced expiratory volume in 1 second. The diagnosis is made with a biopsy. One of the most common complications seen in lung transplant patients is the susceptibility to infection (61). The airway is the easiest mode of entry for infectious pathogens (43). When the host is on immunosuppressive medications, the cause of infections can be both opportunistic and nonopportunistic. *Pseudomonas aeruginosa* is the most common bacterial pathogen, and cytomegalovirus is the most common viral infection in lung transplant patients. Slower healing of the bronchial anastomoses and formation of strictures are some of the late complications that may need to be corrected by an additional procedure.

Heart–lung transplantation

Combined heart–lung transplants are performed in cases of pulmonary hypertension with right side heart failure and Eisenmenger’s syndrome. The other indications are multi-organ end-stage disease, congenital abnormalities and amyloidosis (147), and simultaneous end-stage heart and lung disease. One study stated that although lung transplants are performed with a fair success rate, the long-term survival at 10 years is about 29% (129). Hypertension, one of the complications after heart–lung transplantation, should be treated as best as possible (52). Untreated hypertension can lead to end-stage renal failure over time (92) (115).

Dental management for heart, lung and heart–lung transplant patients

The dental management for heart, lung and heart–lung transplant patients is similar to that of other transplant patients, with the main aim being reduction of dental infection in the heart–lung and individual organ transplant patient. There has been positive correlation between periodontitis and risk for myocardial infarction (9, 74, 75, 82). Patients may present with end-stage heart disease as a manifestation of a multitude of other conditions and may be on many medications. 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. The patients awaiting 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 depression properties (125). Patients awaiting cardiac transplantation generally have a very low cardiovascular reserve and hence 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 carried out to plan the duration of treatment, the posture of the patient during treatment and drugs given before or after treatment.

Post-transplant management should consider the risk of infection caused by immunosuppression (17). The host response to periodontal disease and other oral infection is altered and these patients do not

show a strong inflammatory response. It is known that immunosuppression alters bone marrow function, lending these patients highly susceptible to hemorrhage as a result of the neutropenia, anemia and thrombocytopenia. It is stated that the risk of infection is directly proportional to the degree and duration of immunosuppression (21, 123).

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. It is still a concern for oral complications to lead to systemic sepsis in the cardiac and lung transplant patients like other transplant patients and hence the decision on antibiotics must be made with the recommendation of the treating physician (125).

Transplant immunobiology

As we know, the immune system is responsible for fighting infections with bacteria, viruses, fungi and parasites. It is also responsible for rejection of the transplanted organ. The genes that are responsible for coding the antigens that initiate the rejection process are called the major histocompatibility complex. In humans they are called human leukocyte antigens. The human leukocyte antigens are of two types: class I, which is present in the cell membrane of all nucleated cells; and class II, which is expressed by antigen-presenting cells, such as B lymphocytes, monocytes and dendritic cells. The human leukocyte antigens act in rejection either by the humoral or the cell-mediated immune response. Humoral rejection occurs when there are circulating antibodies that are more specific to the donor human leukocyte antigen and this type of rejection typically takes place within days of transplantation (104). Cellular rejection, which is the more common type of rejection, is mediated by T lymphocytes. T-cell activation is the most important step in the initiation of the rejection process. B-cell activation, along with antibody production, also contributes to the rejection process. The activated T cell then binds with the lymphocyte of the foreign molecule, which then triggers the release of interleukin-2 gene expression. Interleukin-2 then permits the entire cascade of T-cell activation, leading to graft destruction. If the process occurs within days to weeks of the surgery, it is acute rejection and can be reversed by altering the immunosuppressive medication or the regimen. Chronic rejection occurs

over months and can be a very slow and irreversible process. Chronic rejection is caused by cell-mediated changes that alter the vascular walls of the grafted organ, resulting in a slow, but continued, destruction (151). Hyperacute rejection is another type of rejection that occurs within minutes to hours of transplantation. This rarely occurs in patients who were previous transplant patients or those who have had multiple pregnancies. The recipient's body develops antidonor antibodies which activate complement, resulting in a massive attack of the grafted organ, causing hyperacute rejection that cannot be reversed (93). Cytokines that are important in transplantation are those that affect the immune system or the graft and thereby affect the success of the transplantation. The cytokines of interest are interleukins, interferons, tumor necrosis factors and transforming growth factors. Of particular interest has been interleukin-2 gene transcription in relation to graft rejection (30, 36, 113). Cytokines, apart from interleukin-2, that have been studied for association with graft rejection are interferon- γ , tumor necrosis factor- α and - β , and interleukin-1 and -4. Experimental models have been studied using the antibodies and soluble receptors to block the actions of the above-mentioned cytokines. The beneficial effects of these agents have been modest, as far as graft survival is concerned, and so similar materials have not been developed for clinical transplantation (3, 53). Some studies have shown that the presence of interleukin-2 and/or interferon- γ is an early indicator of graft rejection, but several other cytokines, such as interleukin-1, -6 and -8, may also be present as a result of the inflammation from surgery (37).

Immunosuppressive agents

Immunosuppressive drugs are used in transplantation to keep the immune response as subdued as possible in order to improve the survival of the graft. Transplant patients are treated with a regimen from this group of drugs for the rest of their life. The immunosuppressive drugs can be mainly grouped into: (i) calcineurin inhibitors; (ii) glucocorticoids; (iii) antiproliferative/antimetabolites; and (iv) biologics (antibodies) (90).

Immunosuppression is performed at three levels. The first level, induction immunotherapy, mostly uses biologic agents (such as lymphocyte immune globulin and thymocyte globulin) and is implemented before transplantation. This is undertaken to reduce the use of calcineurin inhibitors before surgery

because they are considered nephrotoxic. The second level is maintenance immunotherapy made up of a mix of calcineurin inhibitors, glucocorticoids, mycophenolate mofetil and azathioprine (122). The third level is immunotherapy for established rejection. This will include high-dose glucocorticoids and antilymphocyte antibodies (105).

It is important to know the medications used in transplant patients and how they interact with the drugs used in dentistry. It is also important to understand that these patients might not be on immunosuppressors alone but also on other medications for concomitant conditions.

Calcineurin inhibitors

Calcineurin is a protein phosphatase responsible for the activation of interleukin-2, which triggers the growth and response of T cells. Cyclosporine and tacrolimus are the most widely used drugs in the calcineurin inhibitor group (48, 140). These drugs work by targeting the intracellular signal pathways produced as a result of T-cell activation. They act by binding to an immunophilin (an intracellular protein that binds to immunosuppressive drugs), which leads to their interaction with calcineurin to block its phosphatase activity. This leads to gene transcription inactivation, thereby rendering the T lymphocyte unable to respond (83, 133). Tacrolimus is similar to cyclosporine in the mechanism of action, but binds to a different protein for its effect. Both drugs are metabolized extensively by the liver. Drugs that affect the microsomal enzyme, CYP3A, can influence the levels of both of these drugs, for example erythromycin, methylprednisone, ketoconazole, fluconazole, verapamil and nifedipine (54).

Glucocorticoids

Prednisone and other glucocorticoids are used in combination with other drugs for transplant patients. Glucocorticoids bind to receptors inside the cells and cause redistribution of the lymphocytes, thereby reducing the circulating peripheral lymphocyte counts. The receptor complex curtails the nuclear factor- κ B, which increases apoptosis of the activated cells (5). They also reduce T-cell proliferation, along with a decrease in interleukin-2, and also down-regulate interleukin-1 and interleukin-6, thereby curtailing inflammation. They show strong anti-inflammatory properties on components of cellular immunity, but little on humoral immunity. This group of drug is used in all levels of immunotherapy,

based on need and regimen decided by the individual practitioner. It is noted that the long-term use of steroids has significant disabling and life-threatening adverse effects. Their use, in combination with calcineurin inhibitors, has reduced the strength and dosage needed significantly.

Antiproliferative and antimetabolic drugs

Sirolimus (rapamycin) is currently the most widely used drug in this category. It is a relatively new drug and offers much promise for reducing the use of calcineurin inhibitors. It has a long half life of 60 hours compared with calcineurin inhibitors, which have a half life of 10–12 hours (155). Sirolimus acts by inhibiting a protein kinase called mammalian target of rapamycin, a key enzyme responsible for cell cycle progression from G₁ to S phase (21). Azathioprine is a purine antimetabolite and has been used since 1961. It breaks down into active metabolites to inhibit purine synthesis, which is necessary for cell proliferation, and hence a variety of lymphocyte functions are impaired (78). Mycophenolate mofetil acts after hydrolysis to become an inhibitor of inosine monophosphate dehydrogenase (109). This enzyme is required in the *de novo* pathway of guanine nucleotide synthesis. Hence, it limits the proliferation of lymphocytes and modifies its functions.

Antibodies

Antithymocyte globulin acts to deplete the circulating lymphocytes by direct cytotoxicity (18). Monoclonal antibodies act by inducing rapid internalization of the T-cell receptor, hence preventing antigen recognition (79).

Post-transplant infections

Within the group of transplant recipients, the kidney transplant patients seem to show a lower incidence of infections, and the heart and lung transplant patients show higher rates of infection (28, 119). Infection in the transplant patients can be divided into three time points: (i) up to 1 month post-transplantation; (ii) 1–6 months post-transplantation; and (iii) beyond 6 months post-transplantation (58).

In the first month of transplantation, the infectious agents tend to be endogenous organisms from the gastro-intestinal tract and nosocomial agents acquired from the hospital. During the time between

the first month and the sixth month, the infections are more opportunistic because the cellular immunity is extremely reduced as a result of the medications. Cytomegalovirus is the major infectious agent during this time. Oral candidiasis and herpetic infections are also common during this period. After the sixth month, the risk of infection is dependent on the status of the patient up to that time and based on the immunosuppressive status of the patient. Infection during the first 6 months increases the chance of infection thereafter.

It has been believed, for a long time, that gram-negative pathogens were the leading cause of infection in transplant patients, but recently there has been a shift towards gram-positive pathogens being responsible for many infections (141). The principal gram-positive pathogen from the oral cavity is viridans streptococci, which can be transmitted via an infected organ (95). The predominant gram-positive organisms are enterococci, staphylococci and streptococci. The predominant gram-negative organisms are Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* and *Proteus* species) and nonfermentative gram-negative rods (*Pseudomonas aeruginosa*, *Acinetobacter* species). The other bacteria that can cause an infection, although rarely, are *Mycobacterium* species, *Listeria monocytogenes* and *Nocardia* species. Some other rarely encountered organisms are *Mycoplasma hominis* and *Rhodococcus* species (Table 3).

The most feared type of infection in the transplant patient is cytomegalovirus infection. Early reports have shown that mortality related to cytomegalovirus can be as high as 25%. The serologic status of both the donor and the recipient is the key to developing an infection. Bilateral seronegativity reduces the incidence, whereas seropositivity of either the donor or the recipient increases the chance of infection. The frequency of cytomegalovirus infection in solid organ transplant patients varies from 8% in kidney transplant recipients to 50% in pancreas transplant patients (76, 85, 127). The infection is identified by culture or by enzyme-linked immunosorbent assay. The other potential viral infections are from Epstein-Barr virus, herpes simplex virus and varicella-zoster virus.

Antimicrobial medications

Although the patients are under long-term immunosuppressant medications, antimicrobial medications are also used at times, based on patient needs.

Antimicrobial drugs can be used for therapeutic and prophylactic reasons. The term 'therapeutic' means to treat and cure active infection clinically present in the patient. The term 'prophylactic' corresponds to the use of antimicrobials to avoid infection from occurring clinically. For the use of prophylactic antimicrobials, the drug should be nontoxic and the target infection must be common enough to justify the application. The prophylactic antimicrobial medications typically include an antibiotic, an anti-fungal and sometimes an antiviral, as determined by the physician (112). The dose, and duration and choice of regimen, is guided by the type of organ transplanted, duration after the transplant and the clinical status of the patient.

Oral considerations

Transplant patients may present to their healthcare provider with oral health concerns and may be referred to the dental practitioner for management. It is important to understand that the oral complications found in the transplant patients can be caused by rejection, immunosuppression, side effects of the immunosuppressive agents and in the hematopoietic cell transplantation patients caused by graft-vs.-host disease. The presenting lesions of the patients may be infection related in most cases and noninfection related in others. In analyzing the presenting condition, it is important to remember that these patients are immunosuppressed and hence the presenting inflammatory picture may be altered. In most cases it is suppressed, but sometimes the presenting condition may be exaggerated. The oral lesions may be a manifestation of a systemic condition and hence may not have the same pathogens as the most common oral lesions. It is important to perform culture testing before proceeding with elective treatment of the lesion to identify the pathogen. As transplant patients can develop a variety of infections from viral, bacterial, fungal and parasitic organisms, due diligence must be used in management.

The incidence of dental caries is reported to be higher in the young hematopoietic cell transplantation patients, although no definite evidence for the cause has been identified (117). Periodontal health of the transplant patients is compromised and their oral hygiene is also poor. Cyclosporine causes gingival overgrowth that usually starts manifesting as early as 3 months into therapy (35). The most common area of occurrence is on the facial of the maxillary anterior teeth. The gingival overgrowth as a result of

Table 3. Commonly occurring infections in transplant patients

Organ/cell	Viral	Bacterial	Fungal	Miscellaneous
Hematopoietic cell transplantation	Cytomegalovirus, Epstein–Barr virus	<i>Streptococcus pneumoniae</i> , viridans streptococci	<i>Candida albicans</i> , <i>Candida glabrata</i> , <i>Aspergillus</i>	Protozoan infections
Kidney	Cytomegalovirus, herpes simplex virus, Epstein–Barr virus, varicella-zoster virus, adenovirus	<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Pseudomonas aeruginosa</i> , <i>Salmonella</i> spp.	<i>Candida</i> , <i>Aspergillus</i>	Protozoan infections
Liver	Cytomegalovirus, herpes simplex virus, hepatitis B virus, hepatitis C virus, influenza virus	Aerobic gram-negative rods, <i>Enterococcus</i> spp., <i>Staphylococcus</i> spp., <i>Streptococcus pneumoniae</i>	<i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Pneumocystis</i> spp.	Protozoan infections, Toxoplasma
Heart	Cytomegalovirus, herpes simplex virus, hepatitis B virus, hepatitis C virus	<i>Pseudomonas aeruginosa</i> , Enterobacteriaceae, <i>Staphylococcus aureus</i>	<i>Aspergillus</i> spp., <i>Candida</i> spp.	<i>Toxoplasma gondii</i>
Lung	Cytomegalovirus, Epstein–Barr virus, respiratory syncytial virus	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Mycoplasma pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i>	<i>Aspergillus</i> spp., <i>Candida</i> spp.	<i>Toxoplasma gondii</i>
Pancreas	Cytomegalovirus, Epstein–Barr virus	<i>Enterococcus</i> spp., <i>Escherichia coli</i> , <i>Klebsiella</i> spp., <i>Pseudomonas</i> spp.	<i>Candida albicans</i> , <i>Candida kruzei</i> , <i>Candida glabrata</i>	

cyclosporine can be preceded by pre-existing plaque-induced inflammation. Good oral hygiene has been shown to decrease the level of overgrowth (1). This can be achieved with professional care and/or the effective use of oral hygiene aids, such as antimicrobial mouthrinses (56, 57). Patients taking cyclosporine typically show gingival overgrowth, and when cyclosporine is combined with nifedipine (a calcium channel blocker) the overgrowth is exaggerated (86, 145, 146). Nifedipine is usually a choice to go along with cyclosporine because it does not alter the plasma levels of cyclosporine (143). There have been reports of reduction in overgrowth, with a change from cyclosporine to alternative medications (144). Severe gingival overgrowth generally requires gingivectomy for definitive therapy. It has been recommended that the excised gingival tissues should be sent for biopsy, because there have been case reports of malignant tumors and pemphigus vulgaris lesions associated with gingival overgrowth (114).

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 based on clinical presentation alone. Hairy leukoplakia has been reported in organ transplant patients without human immunodeficiency virus infection (143). Varicella zoster virus and Epstein-Barr virus have been identified in oral lesions. Fungal infections have also been of concern in this group of patients. Candidiasis is the most common fungal infection and can present in any form or in combinations with other fungal infections (67). Aspergillosis, mucormycosis, blastomycosis and cryptococcosis are other fungal infections that can be present in the oral cavity, individually or in combination with candidiasis. The standard 'azole-type' treatment might be effective, and sometimes amphotericin B might also need to be included as part of the treatment (101, 102).

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 (12, 14, 20, 72, 145). These conditions may be treated by altering the immunosuppressive regimen, along with chemotherapy and radiotherapy (100). Graft-vs.-host disease manifests itself similarly to the lichenoid lesions in the oral cavity and may also present with ulcerations. Oral lesions, as manifestations of graft-vs.-host disease, are very difficult to treat and require change in the immunosuppression level along with

some topical cyclosporine or azathioprin (49–51). Hence, it is important to assess the status of the patient before any treatment is attempted. Xerostomia is a common feature (as a result of the radiation or the chemotherapy along with mucositis) in patients who have undergone hematopoietic cell transplantation (32). There is no definitive treatment, although palliative medications, such as topical anesthetic in a mixture of an antihistamine and a coating agent, can be used (143).

Conclusions

The need for dental evaluation of transplant patients before transplantation is increasing with the rise in number of transplants being performed. It is important that the dental practitioner has a strong knowledge base in medicine to manage the cell and organ transplant patients effectively. As this group of patients increase in number, their dental needs will also increase. It is important to co-ordinate all dental treatments with the physician because of the possibility that the health of the patients will deteriorate during or after the dental treatment. It is also important to understand the psychological stress that these patients are preparing to undergo, or have been undergoing, and to consider that during treatment planning. As with all patients, achieving excellent oral hygiene may be difficult, but it should be emphasized that oral infections can increase the chance of systemic infections as a result of immunosuppression. Hence, these patients should have regular dental care. Premedication is recommended for the transplanted patients, although its use is empirical. Dental practitioners should be aware of organ transplant recipients being at increased risk of skin and oral cancer and hence should screen them regularly. A sound knowledge of transplant medicine, immunology, pharmacology and their oral implications, along with judicious application of this knowledge, will allow the dental practitioner to provide adequate dental care to the transplant patient.

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