Dental management of the (solid) organ transplant patient

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The need to provide dental care for organ transplant candidates and recipients will increase in conjunction with the continued expansion of the use of organ transplantation. For the transplant candidate, dental care usually requires application of practice standards that fall within the scope of management of the severely medically compromised patient. There are, however, few guidelines and no clinical trials or outcomes assessments that address appropriate care for transplant recipients. Furthermore, despite the high rate of infectious complications among patients who have received organ transplants, there is little evidence that dental disease contributes to this risk. This article reviews the current status of dental care practices that have been recommended and presents a rationale that can be applied as the basis for guidelines and recommendations for the treatment of the organ transplant patient. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:383-9)

The replacement of a failing kidney, liver, heart, or lung through the transplantation of a healthy organ was one of the major medical and scientific accomplishments during the second half of the 20th century. This was made possible by enhanced understanding of the immune system and the development of immunosuppressive drugs that could prevent or delay rejection of the transplanted organ.1,2 Evidence of the advances made in organ transplantation is reflected in the data from the United Network of Organ Sharing and the Organ Procurement and Transplantation Network (OPTN). Between 1990 and 2000, more than 200,000 organ transplant procedures were performed in the United States.3 During this period, the number of transplantations performed annually increased by 45%, from 15,687 to 22,773.3 As of November 2002, more than 80,000 patients were registered on the national organ transplantation waiting list, as compared with 21,914 in 1990 (OPTN data as of November 20, 2002). There are currently 256 organ transplantation centers in the United States that provide single- or multiple-organ transplantation programs (OPTN data as of November 20, 2002).

Data collected during 1994 and 1995 revealed that 5-year survival rates range from 51% for recipients of heart-lung transplants to 91% for patients who received a kidney from a living donor.3 The median survival rate after renal transplantation from a living donor has increased, from 17 years in 1988 to 36 years in 1996.4 These trends indicate that, as our knowledge in the biosciences advances and the techniques of transplantation continue to improve, the procedure will have a more successful outcome, will be more frequently applied, and will be more economically feasible.5 Under these circumstances, interactions between the dental practitioner and a patient undergoing transplantation are likely to become a more common occurrence.

PRETRANSPLANTATION DENTAL CARE

The dental care provider may first encounter a candidate for organ transplantation during the pretransplantation evaluation, because the protocols from a number of transplantation centers may recommend or require a dental examination and treatment of any disease.6,7 This is a recommended policy at our institution before heart, kidney, or liver transplantation,8,9 but a review of protocols from other transplantation centers

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in the United States reveals that there is no consensus or standard practice that is currently applied. Among numerous texts that comprehensively address the multiple parameters associated with organ transplantation, only one contains a section dedicated to pretransplantation and posttransplantation dental care issues. A dental evaluation appears to be recommended more frequently before heart transplantation, but a 1990 survey of heart transplantation centers revealed that, among the 41 institutions that responded to a dental questionnaire, 61% requested a dental consultation before the surgical procedure. Before kidney transplantation, Medicare provides coverage for a dental examination as a “medically necessary dental service,” but only on an inpatient basis. It has been recommended that this policy be extended to include dental care for all patients undergoing transplantation because of the risk of infection in the immunosuppressed recipient of a transplant.

There are no data or outcomes assessments with respect to the optimal dental management of the candidate for transplantation. The literature also does not provide documentation that dental disease or dental infections have had a significant impact on either candidates for transplantation or recipients of organ transplants. Nevertheless, a number of pragmatic recommendations have been published that are in agreement on several guidelines that are summarized in Table I.

Generally, any dental treatment plan should be based on prudent decisions that ensure expeditious treatment. Major consideration should be given to patients’ previous attitudes toward dental care and their history of oral health self-care. Other factors that may enter into the decision-making process should include the capability of the patient to tolerate dental procedures, the degree of medical instability, and the time constraints dictated by the availability of the donor organ. It should also be noted that, after the transplantation, should situations of financial exigency develop, any concerns regarding the transplant would be given priority over dental care.

These issues may be particularly relevant for a significant proportion of candidates for transplantation in whom a protracted illness related to organ failure may have precluded professional dental care and also contributed to a decline in dental health.

The dental evaluation should also focus on the identification and removal of potential sources of infection. The exacerbation of an infection before surgery could result in the cancellation of the procedure, with the attendant risks of postponement of the transplantation pending resolution of the infection and additional delays for the procurement of another compatible and suitable donor organ. Infection, which can be caused by malnutrition, abnormalities in complement protein synthesis, and impaired phagocytosis, is one of the leading causes of morbidity and mortality in patients with end-stage liver disease. Furthermore, the transfer of any pre-existing infection to the patient immediately after the transplantation, when he is highly immunosuppressed, could lead to devastating consequences. During this time and over a period of several weeks, a regimen of more intense so-called induction immunosuppression is used to prevent acute graft rejection, but this also renders the patient more susceptible to infection and sepsis, which increases the morbidity, mortality, and risk of graft rejection. A dental procedure in the period immediately after transplantation could also create the opportunity for a number of unrelated adverse complications. For example, the aspiration of saliva, particularly if it is contaminated with fungal organisms, could cause life-threatening pneumonia.

The need for dental intervention in the candidate for organ transplantation creates a number of significant dental-medical management predicaments because the failure of 1 or more organs is the major criterion for transplantation. A number of concurrent medical conditions are also likely to be present that either contributed to the organ failure or developed as a consequence thereof. The failure of 1 organ will usually lead to a cascade of complications. For example, end-stage renal disease is often accompanied by poorly controlled diabetes and cardiovascular disease. End-stage liver or kidney disease may lead to multiple metabolic and coagulation disorders that create particularly confounding challenges to dental treatment. Two sources comprehensively address the appropriate dental management of patients with these medical complications. It is also recommended that consultation be initiated with the patient’s physician or transplantation coordinator, or both, before any invasive dental procedures are undertaken.

Data on the dental health status of candidates for organ transplantation are scarce. One study revealed that not only did all 45 patients receiving renal dialysis

<table>
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<th>Table I. Pretransplantation dental care guidelines</th>
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<tr>
<td>Consult with patients’ physician.</td>
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<tr>
<td>Perform dental prophylaxis.</td>
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<tr>
<td>Treat all active dental disease.</td>
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<tr>
<td>Postpone elective treatment.</td>
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<tr>
<td>Remove all potential sources of acute or chronic infection, including partially erupted third molars.</td>
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<td>Remove all nonrestorable teeth.</td>
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<tr>
<td>Perform necessary denture adjustments.</td>
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<tr>
<td>Reinforce oral hygiene and home care instructions.</td>
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<tr>
<td>Initiate daily antibacterial mouthrinses.</td>
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have evidence of some degree of periodontal disease, but 64% had a high index of decayed, missing, or filled teeth. Because approximately 50% of candidates for transplantation are 50 years of age or older, it is more likely that they will have a greater prevalence of dental/periodontal disease. Despite the lack of definitive data, there are a number of indicators that increase the probability that these patients will have poor, rather than good, dental health. Acute or chronic organ failure, with its accompanying complications, may result in disability and loss of employment. This, in conjunction with extensive medical expenses, could contribute to a patient’s lack of access to dental care on a regular basis. A British study found that 58% of recipients of a kidney transplant regularly visited a dentist, similar to the 51% of control subjects not undergoing transplantation. Stress, fatigue, depression, prolonged time on the waiting list (which can range from a median of 6.7 months for a heart to 1.8 years for a liver to 3.3 years for a kidney [OPTN data as of August 7, 2002]), and other sources of incapacitation may further compromise a patient’s ability to maintain optimal dental health. Dental symptoms may be underestimated or disregarded, and dental evaluations may be postponed because of a patient’s preoccupation with their primary disease(s) or symptoms. Xerostomia has been associated with renal failure and dialysis and is a side effect of medications that are likely to be used for the management of complications that accompany major organ failure. This may be another factor that can contribute to dental caries and periodontal disease in the candidate for transplantation. Alcoholic liver disease is one of the most frequent indications for liver transplantation in the United States. Data collected between 1988 and 1998 from liver transplantation centers reveal that 23% to 34% of these transplantations were performed on patients who had alcoholic liver disease. The excessive use of alcohol is frequently associated not only with dental neglect but also with heavy smoking, a risk factor that could further contribute to periodontal disease. Liver transplantation is also increasingly indicated to treat hepatitis C. Because this disease is often associated with drug and alcohol abuse, concurrent smoking and dental neglect are also likely.

### POSTTRANSPLANTATION DENTAL CARE

Before the transplantation, patients and their families undergo an orientation process that involves posttransplantation instructions for daily activities, medication regimens, and precautions. They are instructed to be especially watchful for the signs and symptoms of infection and rejection. Initial postoperative management is coordinated by the transplantation center, but after the graft has stabilized, patients return to their homes, where follow-up care is provided by their primary care physician, in consultation with a regional transplantation center or the primary transplantation center, as needed.

The recipient of a transplant is likely to have fewer and less complex medical-dental management predicaments, but the dental practitioner may still be confronted by a number of other issues. Among these are metabolic derangements, including electrolyte disturbances and diabetes, which may be caused by the immunosuppressive drugs. The patient’s immunosuppressive therapy protocol may include the use of corticosteroids, which the dentist will also need to address.

Recommendations for posttransplantation dental care have been published and are summarized in Table II.

#### Infection

Posttransplantation infection by bacteria, viruses, or fungal organisms is the most common cause of mortality in the immunosuppressed recipient of an organ transplant. This risk is greatest immediately after transplantation because maximal immunosuppression is required for several weeks to months (induction period), when the transplanted organ is most susceptible to rejection. Infection can arise in the organ donor or the organ or because of the surgical transplantation procedure with its attendant complications, wound infection, and postoperative support systems (eg, intravenous lines, catheters). The subsequent likelihood of infection is proportional to the degree of immunosuppression required to prevent rejection. As the risk of this complication subsides, lower levels of maintenance immunosuppression can be implemented. However, the optimal degree of maintenance immunosuppression is

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<td><strong>Immediate posttransplantation period</strong></td>
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<tr>
<td>Consultation with the physician/transplant coordinator</td>
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<tr>
<td>Emergency care of dental infections only</td>
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<tr>
<td><strong>Stable posttransplantation period</strong></td>
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<tr>
<td>Consultation with the physician/transplant coordinator</td>
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<tr>
<td>Frequent recall and prophylaxis</td>
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<td>Daily antibacterial mouth rinses</td>
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<tr>
<td>All indicated dental care</td>
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<tr>
<td>No NSAIDS</td>
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<tr>
<td>Consideration of antibiotic prophylaxis for invasive procedures</td>
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<tr>
<td>Screening for oral and head and neck cancers</td>
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<tr>
<td>Corticosteroid supplementation, if necessary</td>
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<tr>
<td><strong>Posttransplantation rejection period</strong></td>
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subject to patient variability and often must be empirically applied.\textsuperscript{20} For example, inadequate immunosuppression may become evident when coincidental signs of declining organ function or manifestations of rejection begin to appear. On the other hand, excessive immunosuppression may be manifested by an increased susceptibility to infection or an inability to control an existing infection.

Despite these factors that augur poor rather than good dental health among candidates for organ transplantation, there is very little documentation that dental disease is a source of infectious complications after transplantation. Recipients of transplants are closely followed and monitored for the remainder of their lives, and a large number of patients are participating in protocols that are evaluating treatment outcomes. This should provide a substantial patient database from which the relative rate and risk of infections from dental sources can be identified. Nevertheless, the extensive body of current literature that has examined the complication of infection in recipients of organ transplant contains only occasional references to dental infections. It can therefore be assumed that these few cases are reflective of the relative rarity of these occurrences rather than of the failure to diagnose the source of the infection. The reports that have identified dental infections include 3 cases of dental abscesses that occurred among 128 patients who had undergone renal transplantation.\textsuperscript{36} These patients, however, were immunosuppressed only with high doses of corticosteroids, which may have been a predisposing factor. Another report cites 2 cases of infection with \textit{Actinomycetes odontolyticus} in a recipient of a heart transplant and a recipient of a heart-lung transplant. The suspected causes were periodontal disease and aspiration.\textsuperscript{37} One retrospective study of 74 recipients of heart transplants found no significant differences in mortality, infection, or graft rejection rates between patients who were preoperatively treated for foci of dental disease and those who were not.\textsuperscript{38} Other references that are based on in-depth reviews of infections in recipients of organ transplants do not cite dental infection as a cause of posttransplantation sepsis.\textsuperscript{21,35,39-43} The apparent lack of a consensus on the necessity for a pretransplantation dental evaluation also suggests that dental infections do not appear to be a major concern for the health care specialists who are involved with all aspects of organ transplantation.

Medications that are used to prevent organ rejection primarily affect the subsets of the T lymphocytes and the cytokines that regulate these lymphocytes.\textsuperscript{44} It has been suggested that the calcineurin inhibitors cyclosporine and tacrolimus, in addition to other antirejection drugs currently in use, pose considerably less risk for infection than the chemotherapeutic regimens that cause neutropenia in patients undergoing bone marrow transplantation or conventional immunosuppressant high-dose corticosteroids and azathioprine.\textsuperscript{45} Unlike the recipient of bone marrow, however, recipients of organ transplants must be indefinitely immunosuppressed.

The apparent lack of evidence that sepsis originates from dental sources may be primarily attributed to the sparsity of references in the literature rather than to data from clinical studies. This lack of documentation may be related to the fact that most dental infections are not caused by particularly virulent or resistant strains of bacteria and continue to respond to routine antibiotic regimens. As a consequence, these infections may go unreported.

The dental practitioner may also encounter infections caused by herpes simplex virus 1 and \textit{Candida albicans}, which usually originate in the oral cavity and oropharynx. It has been observed that herpes labialis is the most common clinical manifestation of reactivation of the virus after transplantation, with severe manifestations and slow healing.\textsuperscript{21} The prevention and control of these viral and fungal infections are usually accomplished by the prophylactic administration of acyclovir and nystatin, respectively.\textsuperscript{*}

**Endocarditis**

Sporadic cases of infective (bacterial) endocarditis have been reported after heart and other organ transplants,\textsuperscript{47} but this is considered to be a rare complication, even in recipients of heart transplants.\textsuperscript{48,49} Other infectious complications that have occurred in recipients of heart transplants have not been caused by oral flora and did not appear to originate from dental sources,\textsuperscript{50} and none of the cases developed as a consequence of a dental procedure.\textsuperscript{48,49} A study that compared infection in recipients of heart transplants who had and who had not received preoperative dental care revealed no difference in the rates of infection between the 2 groups.\textsuperscript{38}

**Bacteremia and septicemia**

\textit{Streptococcus viridans} has been isolated from blood and cerebrospinal fluid cultures and has been implicated as the cause of septicemia, but only in patients with neutropenia who were undergoing bone marrow transplantation.\textsuperscript{51} Species of \textit{Lactobacillus} organisms have been identified as the cause of bacteremia in recipients of solid-organ transplants.\textsuperscript{52-54} The sources of these bacteremias, however, were the intestinal and

\textsuperscript{*The antifungal fluconazole should not be given to patients who are immunosuppressed with cyclosporine or tacrolimus.\textsuperscript{46}}
genitourinary tracts, and the use of antibiotics before transplantation may have been a contributing risk factor.53

An evaluation of possible infections in the biliary system by invasive procedures, especially in immuno-suppressed patients, has been shown to cause the translocation of bacteria from these sites to the blood stream and become a source of sepsis.55-57 Prophylactic antibiotic therapy, especially during biliary tract manipulation in these patients, has been effective in the prevention of systemic infection.57-59

Premedication

Postoperative guidelines for recipients of solid-organ transplants frequently advise medication with antibiotics before dental procedures,10,60-65 but there are no evidence-based data from controlled clinical trials to support this recommendation, nor is a consensus evident. One reference that is cited as a basis for premedication is a report of 22 patients with nonlymphocytic leukemias who developed periodontal and dental infections in conjunction with chemotherapy-induced neutropenia.66 These complications, however, are less relevant to the situation of the recipient of a solid-organ transplant.45 Another study of recipients of liver transplants has recommended that routine antibiotic prophylaxis not be instituted because of the risk for infection by opportunistic organisms, particularly fungi.67 The use of prophylactic antibiotics also raises concerns about potential adverse interactions among some antibiotics and the drugs used for immunosuppression. Cyclosporine and tacrolimus (Prograf, FK 506; Fujisawa Health Care Inc, Deerfield, Ill) are metabolized by cytochrome P450 enzymes that are in turn inhibited by macrolide antibiotics.56 The administration of these antibiotics could result in increased serum levels of cyclosporine or tacrolimus, thereby increasing the risk for toxicity and infection.46

Other objections to the premedication of recipients of transplants are similar to those raised for patients with heart valve disease, in that it has not been shown to be effective and may generate more risks than benefits.68,69 Nevertheless, bacteremia in the immunocompromised recipient of an organ transplant could lead to sepsis and its management would require antibiotics and the need for further interventions (eg, intravenous lines) that compound the risk for additional complications. Furthermore, poor dental health, which is more likely in the recipient of a transplant, increases the potential for bacteremia. Adherence to the current American Heart Association guidelines that recommend a single-dose premedication regimen70 should minimize the concerns for adverse drug interactions. In addition, compliance with the indications for premedication (ie, that it be given only before the specified invasive surgical and periodontal procedures70) would limit the number of situations for which these patients need to receive antibiotics.

The commitment made by patients, their families, and health care providers to undertake a life-saving organ transplantation requires the most appropriate interventions should serious complications such as rejection or infection occur. An unambiguous rationale for the appropriate use of prophylactic antibiotics for specific dental treatments is also justified unless or until it is shown by controlled clinical studies to be inappropriate or ineffective.

Pain management

Nonsteroidal anti-inflammatory agents should not be used in recipients of organ transplants. These drugs have the potential to exacerbate gastrointestinal disorders, particularly gastric ulcer and acid reflux, which are conditions commonly associated with the administration of corticosteroids.46 These nonsteroidal anti-inflammatory agents may also potentiate the nephrotoxic effects of cyclosporine and tacrolimus.46

Malignancies

During the evaluation of the recipient of an organ transplant, the dental practitioner should be aware of the possibility of malignant lesions that tend to develop on the skin of the head, neck, and lips.71 These tumors include squamous and basal cell carcinomas, particularly in patients with a history of sun exposure.72,73 Recipients of transplants are also at greater risk of oral cancers, and this may be particularly applicable to recipients of liver transplants, who are more likely to have a history of tobacco and alcohol abuse.73,74 The pathophysiologic processes that contribute to the development of these malignancies appear to be multifactorial and may include suppression of the body’s inherent immune mechanisms against malignant cells and activation of papilloma and other oncogenic viruses.71

Cyclosporine-induced gingival hyperplasia

Cyclosporine-induced gingival hyperplasia has received extensive attention in the dental literature,75 but the new generation of immunosuppressive agents has not been shown to cause gingival hyperplasia.

CONCLUSIONS

The need for dental evaluations and treatment of patients before organ replacement is likely to increase in proportion to the expanding use of transplantation to replace failing organs and other structures. A dental examination before transplantation is a prudent recommendation, and treatment should be focused on the
elimination of potential sources of infection that could jeopardize the surgical procedure or cause significant complications during the period immediately after transplantation. Dental treatment may have to be significantly modified for transplant candidates in light of their severely compromised health status.

Complications after organ transplantation consist primarily of infection and rejection. Infections from dental sources are either rare or have not been reported because they could be readily managed. Bacteremia arising from invasive dental procedures represents a significant potential degree of risk in the immunocompromised patient, and premedication is usually recommended despite the fact that its use is empirical and has not been proved to be effective.

Dental practitioners also need to be aware that recipients of an organ transplant are at increased risk for skin and oral cancers, for which these patients should be screened at regular intervals.

The most appropriate manner for providing optimal dental care in conjunction with all of the ramifications associated with organ transplantation remains to be determined. Guidelines should be developed that are based on continued observation and documentation from patient experiences, the accumulation of evidence-based data, and comparisons of outcomes from controlled clinical trials.

REFERENCES


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