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**Reviews**

# SOLID ORGAN TRANSPLANT CANDIDATES AND RECIPIENTS: DENTISTS' PERSPECTIVE

## ABSTRACT

In recent years, dental treatment need in organ transplant candidates and recipients increased in proportion to the increased number of organ transplantations due to advances in immunosuppressive drugs and medical surgical technology.

For the transplant candidates and recipients, dental treatment usually requires standard practice procedures that apply to the management of the severely medically compromised patient. However, there are no guidelines, clinical trials or outcome assessments on appropriate dental treatment for these patient groups. Moreover, medicine often forgets dentistry, as there is no consensus among medical transplant specialists as to whether dental infections pose a risk to organ transplant candidates and recipients.

The aim of this article is to briefly review the most common oral manifestations in solid organ transplant candidates and recipients, and to suggest a specific dental management protocol to guide medical and dental professionals for general dental management before and after solid organ transplantation.

**Keywords:** Solid organ transplantation, oral manifestations, dental management.

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## INTRODUCTION

Transplantation, the replacement of a failing organ, tissue or cellular element with another from a donor for therapeutic purposes, is considered one of the most important achievements in medicine and science in the late 20th century.[1,2] This has been made possible by gaining further insight on the immune response, the improvement of immunosuppressive drugs so as to prevent or delay the rejection of the transplanted organ, and the advances in medical surgical technologies and techniques.

Currently in Turkey, all organ transplantation centres and operations are under the control of the National Tissue and Organ Transplantation and Dialysis Coordination Centre affiliated to the Ministry of Health. According to the data on the number of transplantations, donors, and centres in the last 10 years available on the website of the Ministry of Health, mostly solid organ transplantation (SOT) (kidney and liver) is performed in the majority of organ transplantation centres across Turkey.

As our scientific knowledge continues to increase and transplantation techniques improve, the transplantation procedures will have more successful outcomes, will be performed more frequently, will become economically feasible, and the life expectancy of transplant recipients will increase significantly. As a result, contacts between the dental practitioners and SOT patients are likely to become more often.[1-3] Therefore, the dentist should have knowledge on the specific dental management of these patients.

This article briefly reviews the oral manifestations in SOT candidates and recipients, and suggests a specific dental management protocol by reviewing the literature on general dental management before and after SOT.

### Oral Manifestations in Solid Organ Transplant Candidates

The likelihood of untreated dental disease and poor dental health is increased in SOT candidates due to a number of factors. Disability and loss of employment as a result of organ failure and accompanying complications may result in patients not having regular access to dental care. In addition, stress, anxiety, fatigue, depression, cognitive impairments, substance abuse, and other incapacitation sources may further compromise the maintenance of optimal dental health.[1,4,5] Preoccupation of the patients with their primary disease leads to underestimation or ignorance of the dental symptoms and postponement of the dental examinations.[1,6]

Renal dialysis patients have been reported to show deficits in oral health behaviour, evidence of periodontal disease, and high decayed, missing, and filled teeth (DMFT) index for various reasons.[7] Haemodialysis, reduction of oral fluid intake, and multiple medication usage for the management of complications accompanying renal failure and dialysis cause xerostomia, which may contribute to and promote dental caries, periodontal disease, fungal and viral infections in the renal transplant candidate.[1,8]

Alcoholic liver disease is one of the most frequent indications for liver transplantation. Heavy alcohol use is often associated with dental neglect as well as heavy smoking which is a risk factor that can contribute to and exacerbate periodontal disease.[1,6] Another indication of liver transplantation is the treatment of Hepatitis C, which is usually in association with alcohol and drug abuse, possibly concomitant smoking, dental neglect, and untreated dental disease.[1,6,9] The use of diuretic agents for the management of the frequently encountered cirrhosis, ascites, and/or oedema complications may reduce salivary secretion, which may promote dental plaque accumulation.[5,6,10] Mood modifiers with anticholinergic activity may be required in liver transplant candidates and may cause a decrease in salivary secretion.[6] The possibility of xerostomia is reported to increase with the number of medications taken. Chronic active hepatitis, autoimmune hepatitis, and primary biliary cirrhosis have also been associated with Sjögren's syndrome which is another cause of xerostomia.[11,12]

High prevalence of deficient dental hygiene, poor oral health, xerostomia, periodontal disease, dental caries, and periapical lesions in the liver

transplant candidates has been reported.[9,13] Oral health status, oral health behaviours, and oral mucosal pathologies of liver transplant candidates were evaluated in two studies by Guggenheimer *et al*.[5,6] The most important determinants of dental disease were detected to be intervals longer than 1 year since the last dental visit, smoking, and diuretic therapy.[6] The most common oral pathologies were reported as fissured tongue, atrophy of tongue papillae, angular cheilitis, and oral candidiasis associated with xerostomia due to diuretic use.[5]

**Oral Manifestations in Solid Organ Transplant Recipients**

Although the survival rate of transplant recipients has increased due to the inclusion of cyclosporine A (CsA) and tacrolimus to the post-transplantation immunosuppressive protocol, SOT recipients become more prone to fungal, viral, and bacterial infections as a consequence of long-term immunosuppressive therapy.[2,3,10,14-16] Oral Candida, Cytomegalovirus (CMV), Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) infections, and Epstein-Barr Virus (EBV) associated hairy leukoplakia were observed in these patients.[1,3,10,17]

Oral ulcerations and stomatitis have been considered a possible post-transplantation complication due to immunosuppressives such as tacrolimus, everolimus, and mycophenolate mofetil (MMF), however the reports on this topic are controversial.[18-21]

An additional side effect of CsA is gingival enlargement, which usually appears within the first 3 months, affects the interdental papillae in the anterior region, while does not appear to affect edentulous areas. Gingival enlargement prevents the maintenance of the oral hygiene causing an increased susceptibility to caries, periodontal diseases, and infections. The frequency of gingival enlargement has been reported to be 7-74.1% in renal, and 22% in liver transplant recipients.[15,22-25] The severity of gingival enlargement has been shown to vary depending on factors such as age (more severe in young patients), gender (more frequent in male patients), genetic predisposition, oral hygiene status, type of drug used, and concomitant drug use (calcium channel blockers).[15,22,24] Other immunosuppressive agents such as tacrolimus, sirolimus, and azathioprine may also cause gingival enlargement.[22,23]

It has been shown that the risk of developing oral malignancy increases following SOT, and a considerable amount of squamous/basal cell carcinoma, and Kaposi's sarcoma cases have been reported.[26-30] The multifactorial development of these malignancies may involve suppression of the inherent immune mechanisms against malignant cells, smoking, and activation of human papilloma virus (HPV) and other oncogenic viruses such as EBV, CMV, HSV8, Hepatitis B and C Virus.[31-33]

The prevalence of tongue pathologies such as fissured, saburral, atrophic, hairy, and geographic tongue have been reported to be high in liver transplant recipients.[2,5,15]

Collecting data on oral health of patients before and after SOT, including dental, periodontal, and oral hygiene findings, Schmalz *et al*.[7] and Ziebolz *et al*.[34] reported that SOT candidates and recipients showed similar dental findings (DMFT index), but worse in comparison to the general population. Additionally, in both groups most of the patients were reported to have pronounced periodontal treatment need.[7,34] Oral hygiene findings were significantly worse in SOT recipients compared to the patients on the waiting list.[34]

**Do the Dental Infections Pose Risk for the Transplant Candidates/Recipients?**

Although the combined effects of increased infection susceptibility, untreated dental disease, and poor dental health theoretically imply that dental infections may pose a considerable risk for the physically debilitated transplant candidates and for immunosuppressed transplant recipients, current literature examining the complication of infection in transplant recipients rarely refers to dental infections.[35-39] The absence or scarcity of similar references indicates that dental infections are not observed, or those observed are not reported.[4,40]

In retrospective studies, significantly higher incidence of post-operative complications, such as infection and transplant rejection, were reported in transplant candidates who did not undergo dental examination and treatment in comparison to those who did.[41,42]

Questionnaire survey studies conducted by Guggenheimer *et al*.[4] in the United States (US) organ transplant centres and by Ziebolz *et al*.[34] in the German organ transplant centres provided information on dental screening and dental infections prior to transplantation procedures. The results of these studies showed that most organ transplant centres (80% and 89%, respectively) routinely requested pre-transplant dental evaluation, although the majority indicated this specifically for certain organs, especially the heart and kidney. The emergence of a dental infection that caused postponement or cancellation of the scheduled transplantation procedure was reported in 38%, and post-transplantation sepsis from a possible dental source in 27% of the US questionnaires.

The increasing number of organ transplantations, in combination with the increasing age of transplant recipients and their longer survival, makes it possible for dental disease to become a more common complication source in the transplant population.[4,16] Standardized protocols regarding pre- and post-transplant dental care based on continuous observation and documentation from patient experiences should be established and implemented to minimize this possibility until further prospective and controlled clinical studies are conducted in the closely supervised and monitored transplant population.[1,4]

## General Dental Management Before and After Solid Organ Transplantation

The dental practitioner may encounter a SOT candidate for the first time during the pre-transplantation evaluation phase, because protocols of some transplant centres require dental examination and treatment of existing dental disease as a part of the pre-transplant evaluation process.

As the extensive transplantation literature does not document that dental disease or dental infections have a critical impact on neither SOT candidates nor recipients, no data or outcome assessments are available regarding the optimal dental management of these patients.[1,6] However, a number of pragmatic recommendations that agree on several guidelines have been published.[1-3,16,43-45] In this context, we strongly recommend the pre- and post-transplantation dental protocols outlined in Tables 1 and 2.

**Table 1.** General dental management BEFORE solid organ transplantation

| |
|---|
| **1. Consultation with the patient's physician**<br>• Concomitant medical conditions that lead to or develop as a result of organ failure<br>(Diabetes mellitus, cardiovascular disease, metabolic disorders, anaemia, anticoagulant use, coagulation disorders) |
| **2. Patient education and motivation to maintain proper oral hygiene**<br>• Education and motivation for proper oral hygiene maintenance<br>• Information about the risks and problems that may be encountered in the oral cavity after transplantation<br>• Starting the use of fluoride compounds and antiseptic mouthwashes |
| **3. Identification of active dental diseases and potential infection foci**<br>• Detailed clinical examination of the dentition, periodontium, oral mucosa, lymph nodes and salivary glands<br>• Pulp vitality testing of all teeth<br>• Radiographic examination including a complete series of periapical radiographs (including edentulous areas) or panoramic radiography supplemented with periapical radiographs |

**4. Elimination of all active dental diseases and removal of all potential acute or chronic infection sources**

- Supra/subgingival plaque removal by scaling, root planning, and curettage
- Restoration of carious teeth with favourable prognosis
- Endodontic treatments
- Extraction of teeth having very deep or extensive caries, more than 5-6 mm pocket depths, furcation defects, endoperiodontal lesions, periapical lesions and teeth requiring root-canal treatment which is technically difficult or with uncertain prognosis
- Removal of residual root fragments, and partially impacted teeth
- Necessary adjustments in existing dentures

**5. Preparation of a detailed written report that the patient has been treated**

**Table 2.** General dental management AFTER solid organ transplantation

| | |
|---|---|
| **1. Immediate post-transplantation period** | **1. Consultation with the patient's physician**<br>Medical conditions resulting from the use of immunosuppressives and corticosteroids after transplantation (metabolic disorders, electrolyte imbalances, diabetes mellitus, hypertension, coagulation disorders, drug interactions)<br>**2. Emergency dental treatment performed in a hospital setting with antibiotic prophylaxis**<br>**3. Palliative and local dental treatment**<br>• Prevention of xerostomia<br>• Education and motivation of the patient to maintain proper oral hygiene<br>• Elimination of the risk factors (smoking, alcohol)<br>• Improvement of the diet<br>• Removal of existing dentures and orthodontic appliances<br>• Dental examination for the risk of malignant lesion development<br>• Prevention from infections |
| **2. Stable post-transplantation period** | **1. Consultation with the patient's physician**<br>**2. Palliative and local dental treatment**<br>• Prevention of xerostomia<br>• Education and motivation of the patient to maintain proper oral hygiene<br>• Elimination of the risk factors (smoking, alcohol)<br>• Improvement of the diet<br>• Removal of existing dentures and orthodontic appliances<br>• Control of gingival enlargement<br>• Dental examination for the risk of malignant lesion development<br>• Prevention from infections<br>**3. Elective dental treatment**<br>**4. Invasive dental treatment performed with antibiotic prophylaxis** |
| **3. Post-transplantation rejection period** | **1. Consultation with the patient's physician**<br>**2. Emergency dental treatment performed in a hospital setting with antibiotic prophylaxis** |

## Pre-transplantation dental care

### *1. Consultation with the patient's physician*

There are a number of concomitant medical conditions that lead to or develop as a result of organ failure in the transplant candidate (e.g. poorly controlled diabetes and cardiovascular disease often accompanying end-stage renal disease, multiple metabolic and coagulation disorders resulting from end-stage liver or kidney disease). Before any dental procedure, consultation with the physician to assess the patient's current medical condition, the required laboratory tests, and also the need for introducing antibiotic prophylaxis or prescription of certain drugs (antibiotics or anti-inflammatory analgesics), as well as their doses, is recommended.[1,2,43-46]

### *2. Patient education and motivation to maintain proper oral hygiene*

Education and motivation for proper oral hygiene maintenance and information about the risks and problems that may be encountered in the oral cavity after transplantation should be given to the patient. Instructions for oral hygiene should be

given and the use of fluoride compounds and antiseptic mouthwashes (e.g. chlorhexidine) should be recommended and started.[1,2,44]

***3. Identification of active dental diseases and potential infection foci***

The exacerbation of an infection prior to the transplantation procedure may result in the postponement or cancellation of the surgery and obtaining another compatible and suitable donor organ may cause extra delays. In addition, if any pre-existing infection is transferred to the immediate after transplantation period, it may have devastating consequences, as a more intense regimen called "induction immunosuppression" is used over a period of several weeks to prevent acute graft rejection. Therefore, dental evaluation prior to transplantation should be focused on the identification and elimination of potential infection sources.[1,4,6,10,42]

For dental treatment planning, a detailed clinical examination of the dentition, periodontium, and oral mucosa along with the head and neck region, including the lymph nodes and salivary glands, is extremely important.[3] Pulp vitality testing of all teeth should be performed. A radiographic examination including a complete series of periapical radiographs or panoramic radiography supplemented with periapical radiographs should be conducted.[2,16,43]

***4. Elimination of all active dental diseases and removal of all potential infection sources***

All active dental diseases should be treated, all potential acute or chronic infection sources should be eliminated, but elective treatment should be delayed.[2,44]

Adequate periodontal health should be maintained by removal of supra/subgingival plaque by scaling, root planning, and curettage. Carious teeth with favourable prognosis should be restored, and endodontic treatments should be performed. Teeth having very deep or extensive caries, more than 5-6 mm pocket depths, furcation defects, endoperiodontal lesions, periapical lesions and teeth requiring root-canal treatment which is technically difficult or with uncertain prognosis should be extracted. Residual root fragments and partially impacted teeth should be removed. If the laboratory tests are abnormal, the use of anti-fibrinolytic agents, local haemostatic measures, plasma or platelet transfusion, and vitamin K should be considered before any dental surgical procedure.[46,47] In haemodialysis patients, the dental treatments are recommended to be performed one day after dialysis.[44] And finally, necessary adjustments should be performed in the existing dentures.

Implant surgery should be postponed until the stable post-transplantation period. If implant treatment is carried out prior to transplantation, care should be taken to allow sufficient time to assess the biological response and osseointegration.[2]

During dental treatment procedures, the prescription of non-steroidal anti-inflammatory drugs (NSAIDs) should be limited or avoided. Pain management should preferably be performed with adjusted doses of acetaminophen.[44,46] The use of antibiotics such as tetracyclines and cephalosporins should be usually avoided or the time period between the doses should be increased.[14] In studies concerning the use of certain anaesthetics such as Lidocaine/Xylocaine, Bennett *et al*.[48] asserted that their use should be avoided if possible or they should be used only by increasing the interval between doses, while Byrne[49] stated that they may be used both in end-stage renal and hepatic disease without changing the doses.

There is increasing evidence on the antibiotic resistance resulting from unnecessary use of beta-lactams and on the significant correlation between antibiotic use and increased risk of fungal infection.[50] Cocero *et al*.[51] concluded that extractions can be performed without antibiotic prophylaxis in liver transplant candidates, and satisfactory healing can be achieved using atraumatic techniques. Similar results were also reported by Pereira *et al*.[47], Helenius-Hietala *et al*.[52], and Perdigão *et al*.[53] Adherence to the American Heart Association (AHA) regimen is recommended if prophylactic antibiotic use is necessary.

***5. Preparation of a detailed written report that the patient has been treated***

A detailed written report should be prepared informing the medical team that the patient has been treated and that his/her dental status will not affect the medical treatment.[44]

**Post-transplantation dental care**

The post-transplantation period is divided into 3 periods as immediate, stable, and rejection period.[1,2]

Transplant patients are treated with immunosuppressive drugs such as CsA, azathioprine, and tacrolimus, often together with glucocorticoids, for the rest of their lives in order to prevent rejection of the transplanted organ. Among the medical problems that the dental practitioner may be co-fronted are metabolic derangements, electrolyte disturbances, diabetes mellitus, hypertension, coagulation disorders, and drug interactions. Clinically, oral manifestations that should be considered may appear in these patients due to immunosuppressive therapy.[1,2] Consultation with the patient's physician is recommended to discuss the overall condition of the patient before any dental procedure in all periods after transplantation.[1,2,44,45]

***"Immediate post-transplantation period"*** (the first three months following surgery), is considered as the maximum life-threatening period. Therefore, only emergency dental treatments should be performed in a hospital setting and with antibiotic prophylaxis after consultation with the patient's physician.[2,44] Essentially, palliative and local dental treatment should be aimed to the prevention of xerostomia (use of mouthwashes containing 0.5% aqueous solution of sodium carboxy cellulose every two hours, synthetic saliva substitutes, sugar-free chewing gum), education and motivation of the patient to maintain proper oral hygiene (use of extra soft toothbrush, fluoride toothpaste, and antiseptic mouthwashes such as chlorhexidine), elimination of the risk factors (smoking and alcohol), improvement of the diet (soft diet, avoiding irritant, cariogenic or excessively hot foods), removal of the dentures and orthodontic appliances, examination for the risk of malignant lesion development, and prevention from infections.[2] Prevention and control of fungal and viral infections is usually carried out by prophylactic administration of nystatin and acyclovir, respectively.[1,54]

In the ***"stable period"*** (more than three months following surgery), elective dental treatment can be performed. However, the optimum time for dental treatment is six months following transplantation.[2] Since the epithelization of the graft anastomosis is not completed and the patient is highly immunosuppressed, antibiotic prophylaxis and laboratory tests are recommended when invasive dental treatment is required.[1,2,4]

Gingival enlargement should be controlled in patients using CsA.[2] Decreasing the dose of CsA or substitution of CsA with alternative new generation immunosuppressive agents such as tacrolimus, sirolimus, rifampicin, or MMF together with meticulous oral hygiene advice are reported to help reduce the frequency and severity of gingival enlargement.[1,23,55,56] However, gingival changes may also occur under tacrolimus or sirolimus therapy and azathioprine and MMF combination therapy may help to reduce the gingival hyperplasia prevalence in transplant patients.[22,23,34,56] In case where the nature of the transplanted organ does not allow for the drug to be replaced or the dose reduced, the treatment should be based on the elimination of the predisposing factors and the maintenance of proper oral hygiene.[2,56] The need for surgical treatment should be carefully evaluated because recurrence was observed in 34% of surgical cases within 18 months.[23]

During the evaluation of a transplant recipient, the dental practitioner should be careful about malignant lesions, including squamous/ basal cell carcinomas[57]. The risk of oral cancer is higher particularly in liver transplant recipients who are more likely to have a history of tobacco and alcohol use.[31,32] Since early diagnosis directly affects the prognosis, strict follow-up is important due to the high risk of malignancy development in this population.[30]

NSAIDs are not recommended to be used in transplant recipients during dental treatment procedures, as they exacerbate gastrointestinal disorders associated with corticosteroid administration, potentiate the nephrotoxic effects of CsA and tacrolimus, and increase bleeding.[1,2,14,44,58] Antibiotics (erythromycin, clarithromycin) and azole antifungals (ketoconazole, fluconazole, and itraconazole) may increase serum CsA levels, resulting in a more severe immunosuppression than desired.[1,2,44,58] Co-trimoxazole, tetracyclines, aminoglycosides, and quinolones are known to have nephrotoxic effects.[1,2] The use of macrolide antibiotics may lead to elevated serum CsA or tacrolimus levels and an increased risk of toxicity and infection.[58] Considering all these facts before prescribing or administering any drug during dental treatment, the dental practitioner should consult with the patient's physician for confirmation of the medical condition and immunosuppression level of the patient in post-transplant periods.

For SOT recipients, post-operative guidelines often recommend antibiotic prophylaxis prior to dental procedures[44], but evidence-based data from controlled clinical trials to support this recommendation or a consensus is not available.[1,4,9] Prophylactic antibiotic use raises concerns about the risk of infection by opportunistic organisms and potential adverse drug interactions.[58] Collaboration with the patient's physician and compliance to the current guidelines of AHA recommending a single-dose regimen minimizes the concerns about adverse drug reactions. Questionnaire surveys of US and German organ transplant centres provided data on antibiotic prophylaxis.[4,34] Most centres (83%) routinely recommended antibiotic prophylaxis before dental treatment for all dental procedures, whether invasive or not, after SOT.

In patients under corticosteroid treatment for a long time, the patient's physician should be consulted to ascertain the need for corticosteroid supplementation before dental treatment to prevent adrenal crisis.[2,44]

***"Transplant rejection"*** may be acute or chronic. In case of rejection, dental treatment should be postponed and only emergency dental treatment should be carried out.[2]

## CONCLUSIONS

Creating a healthy oral environment before transplantation is important as well as maintaining it after transplantation, with a special attention to eliminate oral sources of infection. The lack of consensus on the need for dental assessment before transplantation suggests that dental infections are not considered as a major concern by the healthcare specialists dealing with all aspects of organ transplantation. Based on our own experience as dental professionals, we observe that transplant candidates with dental infection foci are usually referred for dental assessment and treatment only a few days before transplantation procedure, and therefore dental treatments have to be performed under time pressure, so the opinion that "*medicine forgets dentistry*" comes true.

## CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interests.


## *ÖZ*

*Son yıllarda organ nakli adaylarında ve organ alıcılarında dental tedavi ihtiyacı, immünsüpresif ilaçlar ve medikal cerrahi teknolojideki gelişmeler sayesinde artan organ nakli sayısı ile orantılı olarak artış göstermiştir. Organ nakli adayları ve organ alıcılarının dental tedavisi genellikle ciddi sistemik hastalıklara sahip hastaların tedavisi için geçerli olan standart prosedürleri içermektedir. Bununla birlikte, bu hasta grupları için uygun dental tedavi konusunda herhangi bir kılavuz, klinik araştırma veya sonuç değerlendirmesi mevcut değildir. Bunun yanı sıra, organ nakli uzmanları arasında dental enfeksiyonların organ nakli adayları ve organ alıcıları için bir risk teşkil edip etmediği konusunda fikir birliği bulunmamakta ve tıp genellikle diş hekimliğini unutmaktadır. Bu makalenin amacı, solid organ nakli adayları ve organ alıcılarında sık görülen ağız belirtilerini kısaca gözden geçirmek ve solid organ nakli öncesi ve sonrasında genel dental tedavi için tıp ve diş hekimlerine rehberlik edecek spesifik bir dental tedavi protokolü önermektir.* ***Anahtar kelimeler:*** *Solid organ transplantasyonu, ağız belirtileri, dental tedavi*

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