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Immunosuppression and Oral Health; the Implications of Organ Transplantation

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ABSTRACT

Organ transplantation is widely undertaken to improve the quality of life of end-stage organ failure patients. The incidence of acute rejection of allografts has dramatically reduced due to the adoption of ever-evolving newer immunosuppressive drug therapies. Although these drug therapies have allowed the rise of organ transplantation and the reduction in post-operative failure rates, they have also been shown to have impacts on the oral cavity. Organ transplant patients are now more likely to develop oral candidiasis, recurrent ulcerative lesions as well as oral malignancies. It is imperative that a multidisciplinary approach is adopted when treating these patients to ensure that their medical and dental care is synergistic in providing the best long-term maintenance for these patients.

Keywords: Immunosuppression, Transplantation, Oral health, Oral flora

INTRODUCTION

In 1954 the kidney was the first human organ to be transplanted successfully. However, acute rejection has been the major hurdle. In1980s, cyclosporine was introduced that that led to an exponential rise in transplantation [1]. To this day organ transplantation remains one of the most pivotal advancements in modern day medicine due to its resultant improvements not just in the quality of life of end-stage organ failure patients but also improved survival. The use of immunosuppressive drug therapy and their adjuncts is widely undertaken to prevent post-operative allograft rejection. However, these medications tend to have a negative impact on oral health in some patients.

Maintaining the delicate balance of oral flora within the oral cavity is paramount in the prevention of dental as well as systemic infections [2]. This balance is dependent on an individual's innate and adaptive immune response. Therefore, the disturbance of these due to various drug therapies could result in the rise of infective and potentially malignant oral conditions. As a result, the organ transplant patients require specialised dental care, both before undergoing transplantation and in the long-term care following this. They are in a higher risk category for oral infections, but their drug regimen may also mean that special precautions may be required before undergoing routine dental treatment [3]. It is, therefore, vital that a multidisciplinary approach is adopted when caring for these patients. This article aims to review the general effect of immunosuppression on oral health, commonly used immunosuppressive drug therapies and their specific impact on the oral cavity.

GENERAL EFFECT OF IMMUNOSUPPRESSION

The human immune system is crucial in preventing the occurrence of harmful and life-threatening infections. T cells are crucial in countering viral and fungal infections and in

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eliminating cells that are undergoing mutations. T cells are also responsible for causing acute allograft rejection following organ transplantation. This occurs through immune response activation by major histocompatibility antigens (MHC) [1]. MHC cells are responsible for presenting foreign antigens to T cells, which then initiates the T cell-mediated response and results in differentiation into effector cells, which propagate an immune response to the target antigen [4]. In transplantation, alloantigen recognition can occur via two mechanisms: the direct and the indirect mechanism. The direct mechanism involves T cells identifying the MHC molecules directly off the graft dendritic cells that have migrated into the lymphoid tissue. The indirect mechanism involves the recipient's antigen processing cells such as dendritic cells that recognise MHC molecules of the donor organ as a foreign antigen and then subsequently stimulating the host T cells by their presenting the signals1. These responses result in acute allograft rejection, which then dramatically decreases long-term survival of the organ [5].

To reduce the risk of postoperative acute allograft rejection, immunosuppressive agents have been incorporated into the standard treatment of renal transplant patients. Consequently, this suppression of the innate and adaptive immune response results in a drastic increase in susceptibility to viral, bacterial and fungal infections of dental and systemic origin, as well as malignant lesions. Studies have shown that over 80% of patients developed post-operative infections. As many as 40% of post-transplant deaths are a result of infections6. The spectrum of oral infections varies in 3 different phases of post-transplantation period [7,8]. The initial phase of one-month post-transplantation, there is a rise in herpes simplex virus infections (HSV), Candida species, as well as other nosocomial bacteria. During the second phase, i.e. one month till the six months after transplantation, there is a further rise in opportunistic pathogens such as cytomegalovirus, Epstein Barr virus, herpes simplex and candidiasis [7,8]. Finally, in the third phase, i.e., after six months following transplantation, there is an increased risk of malignant lesions over and above an increase in incidence and severity of the above-mentioned infections [7,8]. Summary of all these oral infections can be seen in **Table 1**.

In addition to newly invading pathogens, flare-ups of any underlying dental and periodontal infections could result in severe pain and could pose life-threatening challenges to anaesthetists in a managing airway in the peri-operative period. Therefore, all prospective transplant recipients must undergo a thorough dental assessment before undergoing any immunosuppressive treatment.

Table 1. A summary of oral infective lesions seen in transplant patients.

Bacterial	Fungal	Viral
Acute necrotising ulcerative gingivitis/periodontitis Actinomycosis	*Candida albicans* Acute pseudomembranous candidiasis Erythematous candidiasis	Herpes Simplex Herpetic Stomatitis
	Chronic hyperplastic candidiasis Angular cheilitis Median rhomboid glossitis	Epstein-Barr Infectious mononucleosis Hairy leukoplakia Burkitt's lymphoma
		Cytomegalo virus Ulcerative lesions

Oral infections

The most prevalent viral pathogen seen in transplant patients is HSV, with a prevalence of up to 11.3% [9]. The virus is spread by contact or by droplet and has an incubation period of 5 days. The patients present with prodromal symptoms of malaise, fever, pain and regional lymphadenopathy [10]. Primary herpetic stomatitis presents as a cluster of fluid-filled vesicles that can coalesce on the oral keratinised mucosa and adjacent skin on lips, as seen in **Figure 1**. The vesicles rupture to leave ulcerated areas that can become secondarily infected and can take up to 14 days to resolve. If not treated, the lesions can spread to other sites and in a rare instance, can cause blindness as a result of corneal involvement. Recurrent herpetic stomatitis presents as herpes labialis and is a result of reactivation of latent HSV from the trigeminal ganglion. Treatment involves acyclovir 400-800 mg three times a day depending upon renal function, however, in severe infections intravenous antivirals may be required [11].

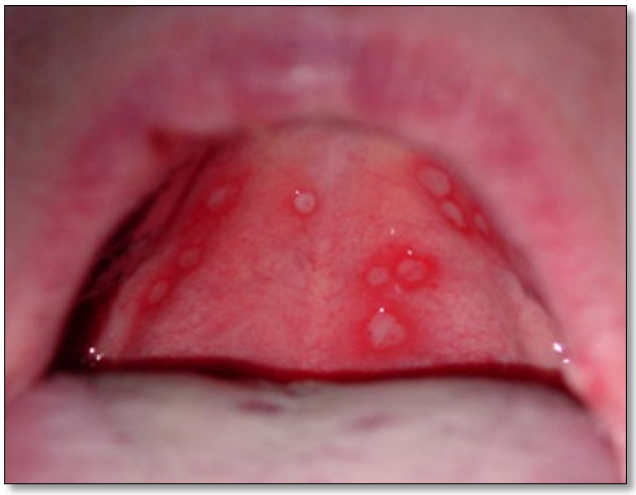

Figure 1. Intraoral presentation of herpes simplex [12].

Oral hairy leucoplakia is also seen in up to 13% of transplant patients due to infection with the Epstein-Barr virus [13,14]. This presents as a corrugated or 'hairy' white lesion on the lateral border of the tongue. These lesions may not resolve that may be a cause of concern; however, these lesions are not known to be premalignant.

Cytomegalovirus infections (CMV) are found in 30-75% of transplant patients, with a variation seen depending on the type of transplant, CMV status of donor and recipient, and the level of immunosuppression [15]. Infection in immune-competent individuals is usually asymptomatic, but in immunosuppressed patients, CMV acts as an opportunistic pathogen and can cause severe CMV mononucleosis [16]. Intraorally, CMV can cause ulcerations on the non-keratinised mucosa including the lateral border of the tongue, the floor of the mouth and soft palate [14].

One of the most common oral manifestations of the effects of immunosuppression is the increase in the prevalence of oral candidiasis, reaching up to 47% in renal transplant patients [8]. Candida is a normal oral commensal in the majority of the population, with *Candida albicans* being the most common cause of oral fungal infections [17]. Species other than *Candida albicans*, such as *C. krusei* are increasingly seen in immunosuppressed patients. Symptomatic candidiasis presents mainly as two lesions:

a) White lesions: Candida leucoplakia, chronic hyperplastic candidiasis.

b) Red lesions: Denture stomatitis, median rhomboid glossitis and angular cheilitis.

The most prevalent form of candidiasis seen in renal transplant patients is acute pseudomembranous candidiasis, with an incidence of 77% [18]. The lesions are characterized by white papules on the oral mucosa that can form thick plaques, as seen in **Figure 2**. These lesions may not resolve and reveal as an erythematous bleeding base [17]. Erythematous candidiasis usually presents on the dorsum of the tongue as red depapillated areas. Chronic hyperplastic candidiasis, on the other hand, presents as a persistent white patch with a rough surface texture. Homogenous and speckled lesions are common, and they arise on the buccal mucosa bilaterally, just inside the commissure. It is important that these lesions are biopsied as 45% of areas show epithelial dysplasia so require close monitoring.

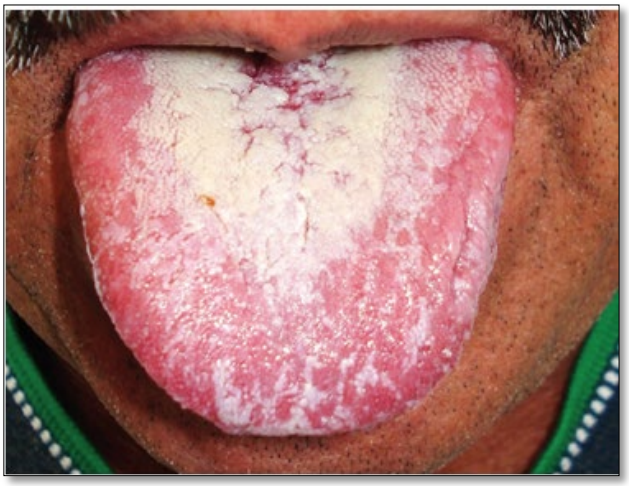

Figure 2. Pseudomembranous candidiasis on the tongue [19].

Median rhomboid glossitis presents as a rhomboidal shaped area of papillary atrophy on the dorsum of the tongue, just anterior of the sulcus terminalis. Although usually asymptomatic, studies have shown these lesions to be present in 11.5% of renal transplant patients [18,19].

Oral malignancies

The development of de novo cancerous lesions is a known risk of transplantation and immunosuppressive therapy. A cell that is undergoing malignant transformation is identified and eliminated in immune-competent individuals; thereby, immunosuppressive therapy poses an increased risk of neoplasia. A study carried out by Collet et al. [20] found that the incidence of *de novo* cancer over a 10 year period was more than twice as high in allograft recipients as the general population. The incidence of malignant lesions ranges from 2.3% to 31% [4]. When comparing the incidence of oral cancer, there were fewer reported cases in kidney transplant patients in comparison to those patients with heart, lung or liver transplants. However, the incidence of lip cancer, however, was highest amongst the kidney transplant patients [20]. Therefore, there is a need for regular dental reviews in order to ensure that no lesions are missed.

Specific effect of immunosuppressive drugs

In addition to higher risk of infections, the immunosuppressive medications are associated with quite specific oral cavity lesions.

Cyclosporine and tacrolimus

Cyclosporine and tacrolimus are calcineurin inhibitors and potent immunosuppressive drugs [21]. Cyclosporine is a selective immunosuppressant, and it blunts the T-lymphocyte response. Although the precise mechanism is unknown, cyclosporine has also been demonstrated to cause severe gingival hyperplasia. This, in turn, increases the incidence of periodontitis by increasing the difficulty in maintaining meticulous oral hygiene. As a consequence, the gingival hyperplasia results in difficulty when carrying out dental treatment. Studies have shown that the gingival overgrowth is seen within three months of starting treatment [22] and is more prevalent in the anterior mandible, followed by the maxillary anterior buccal mucosa [23]. The incidence of gingival overgrowth is most commonly seen in patients taking cyclosporine (53%) in comparison to those taking tacrolimus (0-30%) [22]. Cyclosporine disrupts the turnover of the gingival fibroblasts by decreasing the activity of lysosomal enzymes and decreasing phagocytosis of the gingival fibroblasts [4], thereby, reduces collagen degradation and collagenase gene expression [25]. As a response to the cyclosporine, gingival fibroblasts increase IL-6 secretion which targets gingival fibroblasts to increase proliferation and collagen synthesis [26]. This suggested mechanism of action can be seen in **Figure 3**. Other medications such as calcium channel blockers that are used as antihypertensive medication also increase the incidence of gingival overgrowth [4]. The overall result is increased collagen deposition and overgrowth of the gingivae, which can be seen in **Figure 4**.

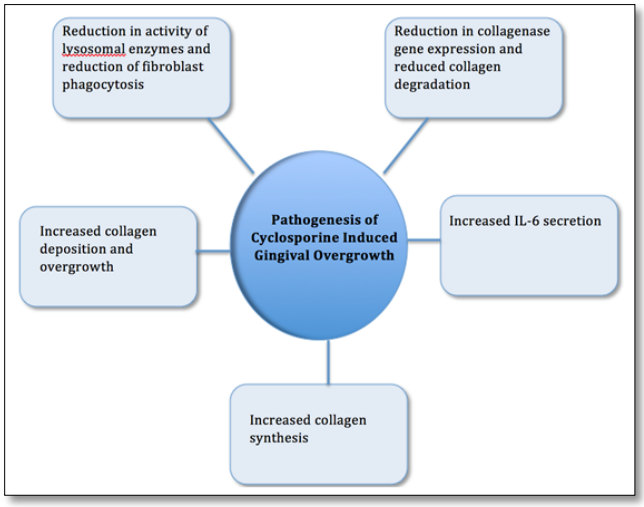

Figure 3. Pathogenesis of cyclosporine A-induced gingival overgrowth: Model depicting the various mechanisms by which cyclosporine A causes gingival enlargement.

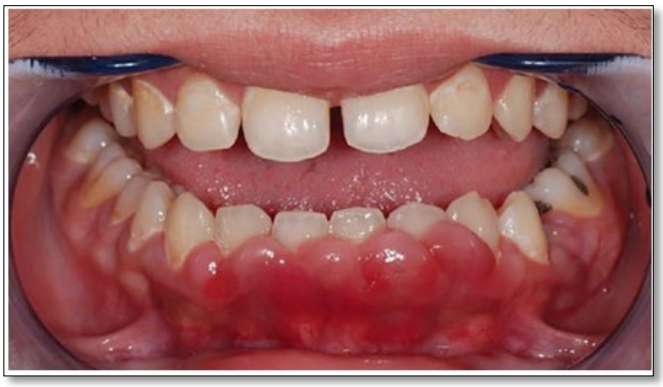

Figure 4. Cyclosporine induced gingival hyperplasia [27].

Tacrolimus has been shown to have similar side effects to cyclosporine; however, the incidence of gingiva hyperplasia is less prevalent. Therefore in patients with severe gingival hyperplasia, switching to tacrolimus is a good solution [28].

Sirolimus

Sirolimus is a target of rapamycin inhibitor, which causes a reduction in T cell and B cell proliferation [29]. In renal transplantation patients it has been shown to reduce the likelihood and severity of graft rejection episodes when compared to azathioprine, and, therefore, it has been widely adopted as an alternative treatment or as an adjunct [30]. However, sirolimus is known to have side effects on the oral mucosa due to its toxicity profile — these most commonly present as areas of stomatitis and aphthous ulceration of the non-keratinised oral mucosa, as seen in **Figure 5**. Studies have shown that aphthous ulceration can be present in 60% of patients [29,31]. Aphthous ulceration typically presents as recurrent ovoid ulcers with circumscribed margins and erythematous halos. They are usually found on the non-keratinised mucosa and are usually 2-4 mm in diameter. They can be preceded with a burning sensation up to 24 h before the emergence of the ulcer [10]. These ulcers cause severe discomfort and therefore can make eating difficult. Treatment involves the use of anti-inflammatory and analgesic mouthwash such as difflam® for symptomatic relief, as well as the use of prednisolone mouthwash, to reduce of the incidence of recurrence [10]. Sirolimus has also been shown to cause gingival hyperplasia in some patients; however, these were not of clinical significance [28].

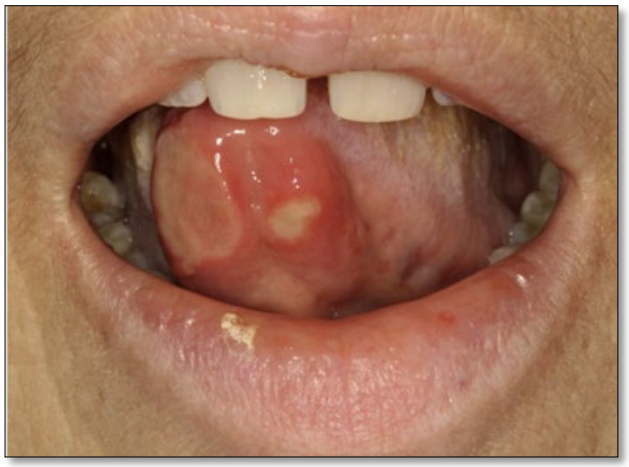

Figure 5. Sirolimus induced ulceration [29].

Corticosteroids

Corticosteroids are employed systemically for long-term use. The use of steroids is associated with an increased risk of periodontitis, dental infections and oral candidiasis has been reported [32]. A study assessed a group of 100 patients on long-term steroid therapy, who had no oral manifestations before commencing treatment. This study found that 19% of patients developed oral candidiasis. There was a significant reduction in mineral bone density and, therefore, made them susceptible to periodontitis and tooth loss [32]. Periodontitis is a localised inflammatory response to bacteria and results in the destruction of the alveolar bone and periodontal ligament that stabilise the dentition. Once a tooth's periodontal support is lost it cannot be regained and will result in tooth loss if not arrested. The need for regular dental check-ups and scaling must be reinforced to reduce the likelihood of tooth loss. **Table 2** summarises the localised effects of some of the immunosuppressive drugs and their adjuncts:

Table 2. Summary of the oral complications of immunosuppressive medication.

Medication	Oral Complications
Tacrolimus	Gingival hyperplasia
Cyclosporine	Gingival hyperplasia
Calcium channel blocker adjuncts	Gingival hyperplasia
Sirolimus	Oral ulceration
Corticosteroids	Candidiasis and periodontitis

CONCLUSION

Implications of immunosuppressive medications on oral health are easy to be overlooked. It is vital that these patients continue to seek regular dental review to prevent complications that are specific to the type of medication. It is essential to follow a multidisciplinary approach in ensuring that patients receive a dental assessment before commencing treatment to reduce the impact of increased infection risk to offer the best holistic care possible.

REFERENCES

1. Ingulli E (2008) Mechanism of cellular rejection in transplantation. Pediatr Nephrol 25: 61-74.
2. Asikainen S, Alaluusua S (1993) Bacteriology of dental infections. Eur Heart J 14: 43-50.
3. National Institute of Dental and Craniofacial Research (2011) Dental management of the organ transplant patient. Available from: https://www.in.gov/isdh/files/OrganTransplantProf.pdf
4. Nappalli D, Lingappa A (2015) Oral manifestations in transplant patients. Dent Res J (Isfahan) 12: 199-208.
5. Matas AJ, Gillingham KJ, Payne WD, Najarian JS (1994) The impact of an acute rejection episode on long-term renal allograft survival (t1/2). Transplantation 57: 857-859.
6. Eun SC (2013) Composite tissue allotransplantation immunology. Arch Plast Surg 40: 141-153.
7. Parisi E, Glick M (2003) Immune suppression and considerations for dental care. Dent Clin North Am 47: 709-731, vii.
8. López-Pintor RM, Hernández G, de Arriba L, de Andrés A (2013) Oral candidiasis in patients with renal transplants. Med Oral Patol Oral Cir Bucal 18: e381
9. Sollecito TP, Pinto A, Naji A, Porter D (2008) Burket's oral medicine. Transpl Med. 11th Edn. pp: 461-480.
10. Scully C (2013) Oral and maxillofacial medicine. 3rd Edn. Edinburgh: Churchill Livingstone/Elsevier.
11. Zuckerman R, Wald A (2009) AST infectious diseases community of practice. Herpes simplex virus infections in solid organ transplant recipients. Am J Transplant 9: S104-107.

12. ENT USA (2013) Oral pathology. Available from: http://www.entusa.com/oral_photos.htm

13. la Rosa-García E, Mondragón-Padilla A, Irigoyen-Camacho ME, Bustamante-Ramírez MA (2005) Oral lesions in a group of kidney transplant patients. Med Oral Patol Oral Cir Bucal 10: 196-204.

14. Spolidorio LC, Spolidorio DM, Massucato EM, Neppelenbroek KH, Campanha NH, et al. (2006) Oral health in renal transplant recipients administered cyclosporin A or tacrolimus. Oral Dis 12: 309-314.

15. Preiksaitis JK, Brennan DC, Fishman J, Allen U (2005) Canadian Society of Transplantation Consensus Workshop on cytomegalovirus management in solid organ transplantation final report. Am J Transplant 5: 218-227.

16. López-Pintor RM, Hernández G, de Arriba L, Morales JM, Jiménez C, et al. (2009) Oral ulcers during the course of cytomegalovirus infection in renal transplant recipients. Transplant Proc 41: 2419-2421.

17. Soams J, Southam J (2005) Oral pathology. 4th Edn. Oxford University Press.

18. Güleç AT, Haberal M (2010) Lip and oral mucosal lesions in 100 renal transplant recipients. J Am Acad Dermatol 62: 96-101.

19. Krishnan PA (2012) Fungal infections of the oral mucosa. Indian J Dent Res 23: 650-659.

20. Collett D, Mumford L, Banner N, Neuberger J, Watson C (2010) Comparison of the incidence of malignancy in recipients of different types of organ: A UK Registry audit. Am J Transplant 10: 1889-1896.

21. McCaughan G (2007) Molecular approaches to the side effects of immunosuppressive drugs. Transplantation 78: 1114-1115.

22. Ciavarella D, Guiglia R, Campisi G, Di Cosola M, Di Liberto C, et al. (2007) Update on gingival overgrowth by cyclosporine A in renal transplants. Med Oral Patol Oral Cir Bucal 12: E19-25.

23. Ghafari A, Poorabbas R, Takieh JA, Sepehrvand N, Kargar C, et al. (2010) Gingival enlargement and its risk factors in kidney transplant patients receiving cyclosporine A. Iran J Kidney Dis 4: 66-70.

24. Wright G, Welbury RR, Hosey MT (2005) Cyclosporin-induced gingival overgrowth in children. Int J Paediatr Dent 15: 403-411.

25. Kim JY, Park SH, Cho KS, Kim HJ, Lee CK, et al. (2008) Mechanism of azithromycin treatment on gingival overgrowth. J Dent Res 87: 1075-1079.

26. Ciavarella D, Guiglia R, Campisi G, Di Cosola M, Di Liberto C, et al. (2007) Update on gingival overgrowth by cyclosporine A in renal transplants. Med Oral Patol Oral Cir Bucal 12: E19-25.

27. Ponnaiyan D, Jegadeesan V (2015) Cyclosporine A: Novel concepts in its role in drug-induced gingival overgrowth. Dent Res J (Isfahan) 12: 499-506.

28. Bharti V, Bansal C (2013) Drug-induced gingival overgrowth: The nemesis of gingiva unravelled. J Indian Soc Periodontol 17: 182-187.

29. Villa A, Aboalela A, Luskin K, Cutler C, Sonis S, et al. (2015) Mammalian target of rapamycin inhibitor–associated stomatitis in hematopoietic stem cell transplantation patients receiving sirolimus prophylaxis for graft-versus-host disease. Biol Blood Marrow Transplant 21: 503-508.

30. Machado P, Felipe C, Hanzawa N, Park S, Garcia R, et al. (2004) An open-label randomized trial of the safety and efficacy of sirolimus vs. azathioprine in living related renal allograft recipients receiving cyclosporine and prednisone combination. Clin Transplant 18: 28-38.

31. Sonis S, Treister N, Chawla S, Demetri G, Haluska F (2010) Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer 116: 210-215.

32. Beeraka SS, Natarajan K, Patil R, Manne RK, Prathi VS, et al. (2013) Clinical and radiological assessment of effects of long-term corticosteroid therapy on oral health. Dent Res J (Isfahan) 10: 666-673.