International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 324-331 www.ijdmsrjournal.com ISSN: 2582-6018

Unveiling oral consequences: A comprehensive review of immunosuppressants, adverse effects on the oral cavity

Dr.Renuka Nagarale, Dr.Neetu Kadu, Nehan Shakeel Ansari, Khan Maryam Mohd Zahir, Mohsin Vaghjipurwala

Professor and HOD ,Department of Public Health Dentistry,M.A.Rangoonwala College Of Dental Sciences And Research Centre,Pune,Maharashtra
Associate Professor,Department of Public Health Dentistry,M.A.Rangoonwala College Of Dental Sciences And Research Centre,Pune,Maharashtra
Undergraduate,Department of Public Health Dentistry,M.A.Rangoonwala College Of Dental Sciences And Research Centre,Pune,Maharashtra
Undergraduate,Department of Public Health Dentistry,M.A.Rangoonwala College Of Dental Sciences And Research Centre,Pune,Maharashtra
Undergraduate,Department of Public Health Dentistry,M.A.Rangoonwala College Of Dental Sciences And Research Centre,Pune,Maharashtra

Date of Submission: 15-12-2023 Date of Acceptance: 25-12-2023

ABSTRACT
Immunosuppression refers to actions that diminish the activation or effectiveness of the immune system.Immunosuppression can be achieved through drugs called as immunosuppresants which help to control severe manifestation of allergic,autoimmune and transplant related diseases. Immunosuppresants function by preventing the allograft rejection by preventing/inhibiting cell activation, cytokineproduction, differentiation and proliferation.The utilization of immunosuppresants has revolutionized medical care, playing a crucial role in managing various autoimmune disorders and preventing organ rejection after transplantation. However, while these medications offer remarkable therapeutic benefits, they are not without consequences. This review article delves into a specific and often overlooked aspect of immunosuppressant therapy – its adverse effects on the oral cavity. As an integral part of the human body's defense mechanism, the oral cavity can be significantly affected by the immunosuppressive actions of these drugs. By exploring the range of adverse effects, their underlying mechanisms, and potential management strategies, this review aims to shed light on an essential dimension of patient care that warrants closer attention within the realm of immunosuppressive treatment. Through a comprehensive analysis of the existing literature, this article seeks to enhance our understanding of the complex interplay between immunosuppresants and oral health, ultimately guiding clinicians in providing more holistic and effective care to patients undergoing immunosuppressive therapy.
Keywords: Immunosuppresants,Organ transplant,Caries,Cancer risk,Periodontal changes
Key Message
Immunosuppressants are vital for managing autoimmune disorders and preventing organ rejection, but their impact on oral health is often overlooked. This review reveals their adverse effects and strategies for care.

I. INTRODUCTION

The ability of the body to resist the pathogens like bacteria ,virus & foreign substances is called as immunity. Immunity can be classified into two broad categories; NATURAL/INNATE & SPECIFIC/ADAPTIVE[57].The innate/natural immunity is the first line of defense not having antigen specificity whereas the adaptive immunity responds against the pathogens through antigen specificity. Immunity is governed by the immune system comprising of thymus, bonemarrow, lymph node, spleen & MALT sometimes including HLA(Human Leukocyte Antigen).HLA are complexeswhich are essential in matching the donor & recipient sites during organ transplantation[58].The immune response elicited by the body during organ transplantation is modulated by immunomodulators which consists of immunosuppressants & immunostimulants. Immunosppressants are drugs used control severe manifestation of allergic,autoimmune,transplant related diseases and to avoid transplant rejection. Immunosuppressants while crucial for managing

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 324-331 www.ijdmsrjournal.com ISSN: 2582-6018

various medical conditions, can also lead to a spectrum of adverse effects on the oral cavity, ranging from increased susceptibility to infections to the development of oral ulcers and gingival growth[59].

II. METHODOLOGY

This questionnaire based review article was conducted in accordance with Arksey & O'Malley's 2021 guidelines which proposes six steps that includes 1)Specifying the research question,2)Identifying the relevant literature,3)Selecting studies,4)Mapping out the data,5)Summarizing, synthesizing and reporting the results and 6)including the expert consultation.[1][2]To make sure all the relevant information from each article was included, a thorough search on the google search engine was done using keywords like 'immunosuppressants','oral cavity', immune system',periodontalhealth','microflora','organtransplant','immunosuppression','corticosterioids','cyclosporine','tacrolimus','immunosuppressive drugs'. Two major criteriawere taken into consideration for selection of the articles one being the language of the articles which was English language and its relevance to immunosuppressants with oral cavity. A team of 2 authors was selected to then review the data to rule out the irrelevant articles by screening the title and abstract of all the studies. A separate word document was created consisting of the title,authors,publication dates of all the relevant studies after segregating them from the duplicate ones. A thorough review of all the articles was done and any disagreements were discussed amongst the reviewer.

Mechanism of action

Immunosuppressants work by hampering the functioning of the immune system from damaging healthy cells and tissues by blocking the activity of T-cells (a type of white blood cell) that directly attacks and eliminates foreign molecules from the body.These drugs target intracellular signaling pathways inducedby the activation of T lymphocytes or T-cells and also inhibit calcineurin (an enzyme that activates T-cells of the immune system) which in turn inhibit the function of T-cells.[4]They suppress cell mediated response by inhibiting genes that code for cytokine IL 1 to 6,8 and interferon C resulting in reduced Tcell proliferation. There is suppression of humoral immunity resulting in B cell reduction,Ab synthesis and reduced activation of T lymphocytes.[5]

SIDE EFFECTS

Immunosuppressants has been a savior in the treatment of acute immune rejection & autoimmune diseases however its lifelong use and ability to non specifically suppress the entire immune system has led to increased risk of infection and cancer.

The side effects of these medication include hepatotoxicity, nephrotoxicity, neurotoxicity, hyperlipidemia, hyperglycemia, immunosuppressant rejection leukopenia , PTLD() , pulmonary edema and renal dysfunction. The side effects of these medications observed in the oral cavity include Gingival hyperplasia , risk of neoplasm , poor wound healing , TMJ arthritis, altered cementum deposition , mucocutaneous pigmentation including melanosis, hairy tongue [3][6][7][8]. Burkets textbook of oral medicine also mentions to consider mucormycosis in differential diagnosis of patients on immunosuppresants having large oral ulcers [9].Geotrichosis – Disseminated infections are seen in debilitated patient or in those receiving immunosuppressants(60).

Patients on immunosuppresants are susceptible to local and systemic fungal infections ranging from typically mild to severe opportunistic ones[3].These infections vary from those of Candida species to deep fungal infections by Aspergillus, Cryptococcus neoformans , Fusarium and Trichosporan.[3][6][9][10][34] Parasitic infection caused by Taxiplasma gondii, Pneumocystis carinii, Strongyloides stercoralis can be observed in transplant recipients on immunosuppressants(60).Patients on immunosuppressants may also show evidence of reactivation of certain latent infections such as hepatitis B & C , tuberculosis& human herpes virus 1-8.In such patients several oral manifestations like herpes simples 1&2 varicella zoster, hairy leukoplakia,cytomegalovirus,mononucleosis kaposis sarcoma,gingivostomatitis,herpes labialis can be observed.[3][6][10]

If the facial nerve is affected as in case of varicella zoster it can result in unilateral paralysis of face and oral tissues .[3][10]

Cytomegalovirus infection occurs as medium sized ulceration on the palate and salivary gland in patients on immunosuppressants after pancreatic or renal transplant[3].These may also causes xerostomia and enamel erosion due to nausea, vomiting& diarrhea eventually resulting in caries development.[3][11]

Liver and kidney transplant patient on immunosuppressants show a significantly higher risk of lip dysplasia, lip cancers, squamous cell

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 324-331 www.ijdmsrjournal.com ISSN: 2582-6018

carcinomas, and progression of leukoplakia to squamous cell carcinoma[3][12]

CLASSIFICATION

The immunosuppressive drugs prescribed during organ transplantation are classified in 4 broad categories namely :-[18]

CLASS OF DRUG	EXAMPLES	MECHANISM OF ACTION
Calcineurin inhibitors	• Cyclosporine analogues • Tacrolimus	Inhibitors of intracellular phosphatase required for interleukin 2 production in T lymphocytes.
Non calcineurin inhibitors	• Sirolimus	Inhibitors of mTOR(Mammalian Target Of Rapamycin) activation of lymphocytes, resulting in cell cycle arrest.
Antimetabolites	• Azathioprine • Mycophenolate mofetil	Inhibitors of de novo purine synthesis in lymphocytes.
Corticosteroids	• Prednisolone • Methyl prednisolone	Regulators of gene expression.

CALCINEURIN INHIBITORS

CYCLOSPORINE ANALOGUES

CSA is a cyclic polypeptide medication derived from fungal metabolite Beauveria Nivea . It acts by suppressing the phosphatase activity by inhibiting calcineurin. Clinical indications for cyclosporine are kidney, liver, heart, and other organ transplantation; rheumatoid arthritis; psoriasis; and xerophthalmia[10][23].Renal dysfunction,hypertension,hyperkalaemia,convulsions,hirsutism,hyperlipidemia,gum hyperplasia and cosmetic changes such as “moon face”(cushings syndrome) and buffalo hump are the frequently observed side effects of CSA[6][15][16][21].Oral mucosa is often the first site of manifestation of autoimmune diseases. If a detailed examination of oral mucosa is carried in asymptomatic patient, it may help in early diagnosis and treatment of these autoimmune diseases and would also prevent it from spreading to skin and other organs[6][8].According to a research published in the journal of scientific dentistry in 2016 25-30% of adults and more than 70% of children show drug induced gingival enlargement which is a hypersensitive response to cyclosporine therapy[7].The increase in gingival hyperplasia may be related to plasma concentration of the drug[25].Gingival hyperplasia in anterior labial papilla commonly occurs within 6 months of treatment with cyclosporine analogues and calcium channel blockers[13][14].In comparison to other drugs such as phenytoin and calcium channel blockers CSA causes more fibrotic gingival enlargement[6][13][14].Development of kaposis sarcoma and squamous cell carcinoma can also be observed[20].A recent experimental study done on **rats** proves that on oral administration of csa an abundant formation and alteration of cementum is observed[19].Large and multilobulated fibrous polyps are observed on the lateral border of the tongue, lip& buccal mucosa.[24]

TACROLIMUS

Strepomyces sukubaenis produces tacrolimus which is a macrolide immunosuppressant used in organ transplant patients. It inhibits calcineurin by interacting with an intracellular protein known as FK binding protein[10][26]. Hepatotoxicity , Neurotoxicity Nephrotoxicity , post transplantation diabetes mellitus, elevation of blood pressure, alteration of taste and oral fibrous growth are some of the major side effects of tacrolimus[3][8][26][27][55][56].Diabetes mellitus is observed as complication in patients on tacrolimus is a result of its negative effect on the pancreatic islet beta cells & glucose intolerance[6][8][30][28][29].Diabetes mellitus causes alteration of the oral microflora creating a favorable environment for fungal infections such as mucormycosis[33][34].In comparison to csa the gingival enlargement caused by tacrolimus is less[3].

NON CALCINEURIN INHIBITOR

SIROLIMUS

Sirolimus (rapamycin) is a macrocyclic lactone produced by Streptomyces hygroscopicus[9].

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 324-331 www.ijdmsrjournal.com ISSN: 2582-6018

Site and MOA : mTOR ,protein kinase involved in cell cycle progression (inhibits activity) Sirolimus causes Hyperlipidemia, Hypertriglycemia , Anemia, leukopenia, thrombocytopenia, mouth ulcer, hypokalemia, neoplasm, GI effects, proteinuria and delayed wound healing[17][37][38][39][40][42].
Hypogeuria is very commonly (>10%) observed in patients on sirolimus[55][56].

Xerostomia and decreased salivary secretion leading to detrimental oral health is due to the direct toxic and antiproliferative effect of drug on the parenchymal and stromal elements of submandibular salivary gland[36].

ANTIMETABOLITES
AZATHIOPRINE

Azathioprine is an antimetabolite known to inhibit purine synthesis further leading to inhibition of DNA & RNA synthesis thereby limiting proliferation of B & T cells[9].Triple immunosuppressive therapy regime includes the administration of AZA along with CSA& corticosteroid for reduction of the renal injury caused by csa administration and at the same time maintaining the dose of immunosuppressant required to minimize the occurrence of allograft rejection[45]. It can cause significant increase in risk of neoplasm and infections especially varicella and herpes simplex[46][47].It increases caries susceptibility and has a significant impact on synthesis and secretion of tertiary dentin[43].

MYCOPHENOLATE MOFETIL

MMF is an antimetabolite which is an ester mycophenolic acid. It is given as a prophylaxis against graft rejection and shows positive effects in the reversal of ongoing acute rejection.MOA includes inhibition of inflammation by interfering with purine synthesis[9][48].Mycophenolate mofetil causes severe gingival enlargement thereby increasing the extent of destruction of periodontal support thus resulting in extensive tooth loss[48].Mycophenolate mofetil can cause immunosuppressant rejection leukopenia[49]. An increase in the prevalence of interstitial nephritis is observed with activation of polyoma virus such as BK virus when Mycophenolate mofetil is given in combination with tacrolimus[51][52].MMF when used in combination with other drugs shows various side effects For eg. When mmf is used in combination with cyclosporine or sirolimus an increase in the concentration of plasma drug and levels of plasma is observed resulting in development of multiple oral ulcers[49].However due to neglect in assessment of plasma levels of mmf these cases are often not reported in any of the published case series[49].

CORTICOSTEROID

These are nonspecific type of Immunosuppressants used. They are used in cases of reversal of acute organ rejection. Steroids have anti inflammatory effects and are able to suppress activated macrophages[9]The systemic side effects associated with corticosteroid includes increased risk of diabetes mellitus, decreased protein synthesis,hypertension,bruising,thinningofmucosa, osteoporosis,osteonecrosis,osteopenia,peptic ulcer and increased risk of opportunistic infections[3][11][15][31][32][33][44].All these have secondary effects on the oral cavity[31][32].It increases caries susceptibility and impacts the secretion and synthesis of tertiary dentin[43].Administration of corticosteroid can result in increased plaque accumulation compromising the periodontal status through inflammation, though the anti-inflammatory effects of corticosteroids is on the gingival tissues and not necessarily in the reduction of rate of periodontal breakdown[5][44].Oral candidiasis may also be frequently encountered as side effects of corticosteroid[9]. Fibrous and granulation tissue masses resulting in gingival inflammation, swelling, pyogenic granuloma, or gingival hyperplasia are associated with cyclosporine and corticosteroids[3][7][12][15].
Although the consumption of immunosuppressants cannot be completely avoided however certain precautions can be taken to reduce its side effects.

RECOMMENDATIONS FOR PHYSICIANS

- Prior to immunosuppressive therapy, communication between dental and medical professionals should be established to promote complete patient care. A comprehensive oral examination with periodontal charting, current radiographs, and intraoral photography can document the oral condition at baseline.
- Dental consultation should be considered prior to performing transplant related procedures and prescribing immunosuppressants. Also any elective dental procedures required should be performed in the stable post transplantation period.
- Patients undergoing organ transplantation should have routine dental examination and should be educated about the use of interdental aids and powered toothbrushes after assessment of patients ability of self care

- The patient and the guardian should be taught to perform oral examination at home and monitor his / her oral condition to aid health care professional in early diagnosis of pathology.
- Antifungal and antiviral medications should be prescribed along with immunosuppressants. Herpes virus infected patients can be treated with topical anesthetics and antiviral drugs along with immunosuppressants.
- Treatment success depends on the detection and management of oral changes, appropriate communication with medical professionals, and provision of referrals to dental specialists to effectively treat any complications that arise.

RECOMMENDATIONS FOR DENTIST.

- The dental professionals should be familiar with the interaction between various drugs and immunosuppressants such as patients on CSA must be prescribed clindamycin instead of erythromycin.
- Prescription fluoride toothpaste or fluoride varnish application can help mitigate the impact of acidity on tooth structure resulting from nausea, vomiting, or xerostomia, while mouthwashes like chlorhexidine can be recommended to uphold excellent oral hygiene.
- Drug induced gingival enlargement & severe periodontal pocket can be treated through gingivectomy,flap surgery, laser therapy &changing to drugs with lesser incidence of gingival enlargement such as tacrolimus but it is associated with oral fibrous growth.
- Oral candida infections can be treated with the use amphotericin lozenges, chewable nystatin pastilles, topical miconazole
- The dentist should keep themselves updated with the newer drugs and treatment modalities for effective treatment of the patient and should be competent to detect the various associated pathologies

III. CONCLUSION

In conclusion, this review has provided a comprehensive understanding of the adverse effects of immunosuppressants on oral health. The evidence presented underscores the significant impact of these medications, which can lead to a range of oral health issues, including increased susceptibility to infections, oral mucosal changes, and compromised periodontal health. Recognizing these potential complications is vital for healthcare professionals, particularly dentists and physicians, as it underscores the importance of collaboration and careful monitoring of patients on immunosuppressive therapy.

As we conclude, it is clear that a holistic approach to patient care is necessary, one that includes the close collaboration of medical and dental practitioners. This ensures that individuals on immunosuppressants receive the highest quality of care, with a focus on preventing and managing oral health complications. Additionally, educating patients about the potential risks and the importance of maintaining excellent oral hygiene while on immunosuppressive medications is imperative.

REFERENCES

[1]. Arksey and O'Malley's and Beyond volume 8,2021,101375:Customizations to enchance a team based,mixed approach to scoping review methodology.
[2]. H Arksey,L.O.Malley – Scoping studies methodological framework.
[3]. Effects of immunosuppressive medications on oral health by Denise Kissell,BSDH,EFDA,MFH.
[4]. How do immunosuppressants work by Nazmeen Memon (Rx list).
[5]. Immunosuppressant drugs: Role in periodontium Dec 2016 Journal of scientific dentistry 6(2):60-66 by Seema G,Anjusha Bhadran (IDA).
[6]. Bascones-martinez A,matilla R,Gomez Font R,meurman JH-Immunomodulatory drugys:oral and systemic adverse effects med oral patol oral gingiva buccal 2014;19:e24-e31.
[7]. Al-Mohaya M, Treister N. Calcineurin inhibitor-associated oral inflammatory polyps after transplantation: calcineurin inhibitor-associated oral inflammatory polyps. J Oral Pathol Med. 2007;36:570–574. Pharmacology for dental students and allied health sciences (4th edition) by padmaja udaykumar Essentials of physiology for dental students 2nd edition by K sembulingham and Prema sembulingham. Textbook of Oral medicine 4th edition by Anil Govindrao Ghom and Savita Anil Ghom. Newman and Carranza's Clinical periodontology (Third south Asian edition) US editors Michael G Newman, Henry H takei , Perry R Klokkevold , Fermin A Carranza ; Adaptation editor CD Dwarkanath , N Ambalavanan , DG Naik, A Uppoor , A Jain. Essentials of Pathology for dental

students by Harsh mohan and sugandha mohan

[8]. Arisawa E,Almeida J,Carvalho Y,Cabral L-Clinicopathological analysis of oral mucosa autoimmune disease.med oral patol oral gur guccal 2008;13:E94-7.

[9]. Burkets Oral medicine , thirteenth edition by Greenberg , Glick , Ship.

[10]. Bandora HMHN,Sanaranayate LP-Viral,bacterial and fungal infections of the oral mucosa:types incidence,predisposing factors,diagnostic algorithms and management.Periodontal 2000.2019;80:148-176.

[11]. Lucan VC,Berardinelli L-Gastrointestinal side effects of post transplant therapy.J gastrointestin liner dis 2016;25:367-373.

[12]. Scully C,Bagan JV-Adverse drug reactions in orofacial region.Crit rev oral biol med-2002;15:221-239.

[13]. Said MA,Teixeria e silva LS,de Oliveira Rocha MA,et al-Adverese drug reactions associated with treatment in patients with chronic rheumatic diseases in childhood:a retrospective real life review of a single center cohort.Adv Rheumatol2020;60:53.

[14]. Thomason JM Seymour RA,Ellis JS-Risk factors for gingival overgrowth in patients medicated with cuclosporin in absence of calcium channel blockers. J clin periodontal 2005;32:273-279.

[15]. Oyetola EO,Onotade FJ,Ag belusi GA,Fatusi OA,Sanusi AA.Oral findings in chronic kidney disease;implications for management in developing countries .BMC oral health 2015;15:24.

[16]. Gualtierotti R,Marzano A,Spadari F,Cugno M.Main oral manifestations in immune mediated and inflammatory rheumatic diseases.J Clin med 2018;8:21.

[17]. Lacouture M-Sibaud v toxic side effects of targeted therapies and immunotherapies affecting the skin,oral mucosa,hair and nails.Am J Clin dermatal 2018 nov.

[18]. Essentials of pharmacology for dental students,3rd edition,by KD Tripathi.

[19]. Effect of cyclosporin A on the mineral apposition rate of cementum and dentin in growing rats E-Chih Shen et al. J Periodontol. 2005 Jun.

[20]. Association Between Immunosuppression and Outcomes in Oral Cavity Squamous Cell Carcinoma Julia Chang et al. Otolaryngol Head Neck Surg. 2021 May.

[21]. Cyclosporine. An immunosuppressant affecting epithelial cell proliferation J Kanitakis et al. Arch Dermatol. 1990 Mar

[22]. The effect of cyclosporin on cell division and apoptosis in human oral keratinocytes J Birraux et al. J Periodontal Res. 2006 Aug.

[23]. Inhibition of apoptotic signals in overgrowth of human gingival fibroblasts by cyclosporin A treatment

[24]. Ji-Yeon Jung 1, Yeon-Jin Jeong, Tea-Sul Jeong, Hyun-Ju Chung, Won-Jae Kim

[25]. Gingival anlargements:Differentiatial diagnosis and review of literature.Dr Amit Arvind Agarwal.World journal of clinical cares 2015 sept 16:3(9):779-788.

[26]. The comparative effects of azathioprine and cyclosporin on some gingival health parameters of renal transplant patients.Alongitudinal study.RA Seymour et al. J clin periodontal.1987 Nov.

[27]. Naerens M,Kuypers DR,Sarwal M(February 2009).”Calcineurin inhibitors nephrotoxicity”.Clinical journal of American society of nephrology 4(2):481-508.

[28]. Myers BD,Ross J,Newton L,Luetscher J,Perlroth M:Cyclosporinne associated chronic nephropathy.N Engl J med 311:699-705,1984.

[29]. Vivek Mohanty.Ravi Kant,Aditya sudan,”Tacrolimus induced diabetes presenting as recurrent pyclonephritis-A rare clinical presentation”’Vivel Mohanty,Ravi Kant,Aditya Sudan.European journal of medical and health science,Aug 11,2020.

[30]. Post transplant diabetes mellitus.The role of immunosuppression on RM Jindal et al.Drug saf-1997 Apr National library of medicine-Pubmed.

[31]. “Post-transplant diabetes mellitus:causes,treatment and impact on outcomes”’Jennifer Larsen,Brian Boerner,Vijay Shivaswamy.Endocrine reviews,volume 37,issue 1,1st feburary 2016,pages 37-61.

[32]. “Pilmonary mucormycosis after renal transplantation: A case report and a literature review”’Osama N Dukmark et al .Ann med surg (lond) 2022 june 1.

[33]. Song Y,Qiao J,Giovanni G,Yang H,Wu J,Cheng J.Mucormycosis in renal transplant recipients:review of 174 reported cases.BMC

infect.dist.2017;17doi:10.118679-017-2381-1.

[34]. Downey MR, Taskar V, Linder DF, Baer SL, Waller JL, Bollag WB, Kheda M, Mohammed A, Padala S. Incidence and risk factors for mucormycosis in renal transplant patients. J Investig Med. 2022 Feb;70(2):396-401. doi: 10.1136/jim-2021-001933. Epub 2021 Nov 19. PMID: 34799422.

[35]. Mutalik VS,Bissonnettte C,Kalmar JR,MC Namara KK.Unique oral fungal presentations of deep fungal infections:a report of four cases.Head neck patrol 2020;15:682-690.

[36]. Oral compl,ications associated with immunosuppression and cancer therapies.JB Epstein,AW Chow,Infect Disclin North AM 1999Dec;13(4):901-23.

[37]. SalahA,Laila S,Raksha M,,'The effect of thr immunossupressive deug sirolimus on structure of the submandibular glands of the Rat"'Suez canal university medical journal vol 22(1),2019,page 18-28.

[38]. Timothy F,Sharon V,Dianna W,"Recognition and management of oral mucosal injury caused by mammalian target of rapamycin inhibitors:Acase series."Case rep oncol.2015 may-aug,8(2) 369-377.

[39]. Fricain JC,Cellerie K,Sibaud V,Catros et al(oral ulcers in kidney allograft receipients treate with sirolimus).Ann Dermatol venerol.2008 nov:135(11):737-41.Epub 2008 sep 17.PMID:19061651.

[40]. Fishbane S, Cohen DJ, Coyne DW, Djamali A, Singh AK, Wish JB. Posttransplant anemia: the role of sirolimus. Kidney Int. 2009 Aug;76(4):376-82. doi: 10.1038/ki.2009.231. Epub 2009 Jun 24. PMID: 19553912.

[41]. Hong JC, Kahan BD. Sirolimus-induced thrombocytopenia and leukopenia in renal transplant recipients: risk factors, incidence, progression, and management. Transplantation. 2000 May 27;69(10):2085-90. doi: 10.1097/00007890-200005270-00019. PMID: 10852601.

[42]. Murgia MG,Jordan S,Kahan BD-The side effect profile of sirolimus:a phase 1 study in quiescent cyclosporine prednisolone-treated renal transplant patients.Kidney int 1996;49:209.

[43]. Kido K, Evans RA, Gopinath A, Flynn JD. Severe Hypertriglyceridemia Induced by Sirolimus Treated With Medical Management Without Plasmapheresis: A Case Report. J Pharm Pract. 2018 Feb;31(1):104-106. doi: 10.1177/0897190017692920. Epub 2017 Feb 16. PMID: 28205445.

[44]. Tsvetelina Borisova-Association between steroid anti inflammatory drugs and oral dental state-A literature review.Adv dent and oral health 2019;11(1):555801 DOI:10.19080/ADOH-2019.11.555801,pub:June 11,2019.

[45]. Nadimpalli H,Deepa G,Swati,"Corticosteroids-Assets and liabilities on periodontium",Assan journal of pharmaceutical and clinical research vol 11,issue 8,2018.

[46]. Marc I. Lorber, Stuart M. Flechner, Charles T. Van Buren, Kaye Sorensen, Ronald H. Kerman, Barry D. Kahan, Cyclosporine Toxicity: The Effect of Combined Therapy Using Cyclosporine, Azathioprineand Prednisone,American Journal of Kidney Diseases,Volume 9, Issue 6,1987, Pages 476-484.

[47]. Orlicka K, Barnes E, Culver EL. Prevention of infection caused by immunosuppressive drugs in gastroenterology. Therapeutic Advances in Chronic Disease. 2013;4(4):167-185. doi:10.1177/2040622313485275

[48]. Faten N Aberra, MD, MSCE , Gary R Lichtenstein, MD, Methods to Avoid Infections in Patients with Inflammatory Bowel Disease, Inflammatory Bowel Diseases, Volume 11, Issue 7, 1 July 2005, Pages 685–695, https://doi.org/10.1097/01.MIB.0000160742.91602.b7

[49]. Janina Golob Deeb,Denver J.Lyons,Daniel M,laskin,George R.Deeb-Severe drug induced gingival enlargement and periodontitis:A case series with clinical presentation and management,oral and maxillofacial surgery cases,volume 6,issue 1,2020,100143,ISSN 2214-5419.

[50]. JAAD Case Rep. 2015 Sep; 1(5): 261–263. Published online 2015 Jul 29. doi: 10.1016/j.jdcr.2015.06.005PMCID: PMC4809219PMID: 27051747

[51]. Mycophenolate mofetil-induced oral ulcerations in solid organ transplant recipients: A report of 3 cases Jonathan Salik, MD,a,∗ Randy Tang, MD,b Kristin

Nord, MD,c Paul I. Schneiderman, MD,b and Marc E. Grossman, MD, FACPb

[52]. Asare K, Gatzke CB. Mycophenolate-induced oral ulcers: Case report and literature review. Am J Health Syst Pharm. 2020 Mar 24;77(7):523-528. doi: 10.1093/ajhp/zxz358. PMID: 32058566.

[53]. Gupta, N., Lawrence, R.M., Nguyen, C. et al. Review article: BK virus in systemic lupus erythematosus. Pediatr Rheumatol 13, 34 (2015). https://doi.org/10.1186/s12969-015-0033-9

[54]. Clin Mol Hepatol. 2014 Sep; 20(3): 291–299. Published online 2014 Sep 25. doi: 10.3350/cmh.2014.20.3.291PMCID: PMC4197178PMID: 25320733

[55]. Safety of reduced dose of mycophenolate mofetil combined with tacrolimus in living-donor liver transplantation

[56]. Hyeyoung Kim,1 Nam-Joon Yi,corresponding author1 Juyeun Lee,2 Joohyun Kim,1 Mi-Ra Moon,2 Jaehong Jeong,1 Jeong-Moo Lee,1 Tae Suk You,1 Suk-Won Suh,1 Min-Su Park,1 YoungRok Choi,1 Geun Hong,1 Hae Won Lee,1 Kwang-Woong Lee,1 and Kyung-Suk Suh1

[57]. Sixou JL, de Medeiros-Batista O, Bonnaure-Mallet M. Modifications of the microflora of the oral cavity arising during immunosuppressive chemotherapy. Eur J Cancer B Oral Oncol. 1996 Sep;32B(5):306-10. doi: 10.1016/0964-1955(96)00006-1. PMID: 8944833.

[58]. Godman and Gilamn's the pharmacological basis of therapeutics,13th edition by Bjorn C.Knollman,Laurence Brunton and Randa Hilal-Dandan.

[59]. Oral Dis. 2020 Jan; 26(1): 213–223. Published online 2019 Nov 11. doi: 10.1111/odi.13199 PMCID: PMC6988472PMID: 31532870 Oral adverse effects of drugs: Taste disorders Willem Maria Hubertus Rademacher,corresponding author 1 , 2 Yalda Aziz, 1 Atty Hielema, 3 Ka- Chun Cheung, 3 Jan de Lange, 2 Arjan Vissink, 4 and Frederik Reinder Rozema 1 , 2

[60]. Emmanuelle Vigarias,Joel B,Vincent S,"Oral mucosal changes induced by anti cancer therpies and immune checkpoint inhibitors.Review article,springer-verlag berlin heridelberg 2017.

[61]. Essentials of physiology for dental students,2nd edition,K Sembhulingham, Prema Sembhulingham.

[62]. Essentials of Pathology for dental students,5th edition,Harsh mohan,Sugandha mohan.

[63]. Transplantation,immunology,cellular and molecular immunology,9th edition by Abul K Abbas,MBBS,Andrew H Lichtman,MD,PhD and Shiv Pillai,MBBS,Phd.

[64]. Burkets Oral medicine , Twelevth edition by Greenberg , Glick , Ship.