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Oral Cavity as a Source of Atypical Infective Pathogens in Chronic Kidney Disease Patients

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Abstract

Objectives: To investigate the prevalence of pathogens in mouth samples of immunosuppressed patients with Chronic Kidney Disease (CKD). These patients are susceptible to infections due to accumulated uremic toxins and altered leukocyte function. After kidney transplantation anti-rejection therapy further depresses the immune system.

Method and Materials: Eighteen CKD patients were enrolled to this study. Twelve of them were also previously examined at the predialysis stage between 2000 and 2005, and then followed up until 2015. Clinical and radiographic oral examination was performed; Total Dental Index (TDI) and Periodontal Inflammatory Burden Index (PIBI) were calculated to describe the degree of oral inflammation. Subgingival plaque and whole saliva samples were collected for microbial analyses of bacteria. *Candida* species were detected from oral mucosa.

Results: TDI indicated good oral health in most of the patients. However, culture of bacteria from plaque samples revealed uncommon findings such as *Stenotrophomonas maltophilia, Chryseobacterium meningosepticum*, and *Pseudomonas aeruginosa* in 33% (6/18) of the patients. We found Candida (8/18) which was associated with uncommon bacterial findings (5/8) ($P<0.05$).

Conclusion: Dentists should be aware that a CKD patient´s oral cavity may harbor uncommon immunosuppression related infective pathogens, which are a threat to the patient.

Keywords: Dental plaque; Kidney transplants; Oral health; Saliva

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Introduction

The oral cavity is an important source of infections. Over 700 bacterial species have been detected in the oral microbiome, out of which 30-50% is not yet cultivable [1]. Teeth, periodontium, dentures, and mucous membranes of the mouth and nasopharynx have been considered potential reservoirs for pathogens [2-4], particularly in immunocompromised patients [5].

Patients with chronic kidney disease (CKD) are prone to infections because of immune alterations caused by uremia, related conditions such as diabetes, or because of immunosuppressive treatment. Patients with a kidney transplant have permanent immunosuppressive medication to prevent organ rejection. This increases the risk for infections caused both by nosocomial and opportunistic pathogens. Infection is one of the most common causes for hospital admission and death in recipients of solid organ transplants [6-8]. Even through diseases in the oral cavity, such as periodontitis, dental decay, and other manifestations of poor oral health are common in CKD patients, oral infections and inflammation often remain an overlooked problem.

Microbial analyses of subgingival plaque and whole saliva have been used for detection of specific bacterial species such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Prevotella intermedia*, *Campylobacter rectus,* and *Parvimonas micra,* which all

Table 1: Definition of Total Dental Index (TDI) and Periodontal Inflammatory Burden Index (PIBI).

TDI = Total Dental Index (32 teeth)	
Type of disease	Score
Caries	
no carious lesions	0
1-3 carious lesions	1
4-7 carious lesions or no teeth in maxilla or mandibula	2
≥ 8 carious lesions or radix or no teeth	3
Periodontitis	
4-5mm deep gingival pocket	1
≥6 mm deep gingival pocket	2
pus in gingival pocket	3
Periapical lesions	
1 periapical lesion or vertical bone pocket or both	1
2 periapical lesions	2
≥ 3 periapical lesions	3
Pericoronitis	
absent	0
present	1

PIBI: Periodontal Inflammatory Burden Index (28 teeth); PIBI = Σ (Nmod PPD + 2Nadv PPD); PPD: Pocket Probing Depth; Nmod: Number of Sites with Moderate Periodontal Lesions (4-5 mm); Nadv: Number of Sites with Advanced Periodontal Lesions (≥6 mm).

have been associated with periodontal disease [9]. Bacterial cultures have been used to identify these pathogens. The Polymerase Chain Reaction (PCR) has been used for a direct identification of pathogens in subgingival specimens and also for elucidating the role of specific bacteria. Molecular methods are currently available for the typing and subtyping of bacterial strains in general, but these can vary in efficiency and in the amount of required labor in the laboratory.

Hyposalivation with subsequent xerostomia either due to disease such as diabetes or to the number of drugs used daily may have an impact to oral microbiota especially in the elderly [10,11]. When the host immune defenses are impaired or when the oral microbial flora is disturbed, *Candida albicans* colonization may also be seen in CKD patients [12].

There are only a few longitudinal studies where the aspects of oral health have been followed longitudinally during the course and different treatment phases of CKD [13]. Thus, we have set out to investigate patients from predialysis to dialysis and post-transplantation with the aim to study how immunosuppression impacts oral microbiome even after dental infection foci have been eradicated already at the predialysis stage. We hypothesized that immunocompromised CKD patients harbor atypical pathogens in their periodontal pockets in addition to the common bacterial findings.

Materials and Methods

Patient data

Eighteen patients (13 men, 5 women) with CKD aged 39 to 84 years (mean age 60.6 years) were enrolled to the study. Clinical and radiological oral examination was conducted at the Departments of Nephrology and Oral and Maxillofacial Diseases of the Helsinki University Hospital (HUH), Helsinki, Finland, during the year 2015.

Table 2: Clinical characteristics of 18 adult patients with the chronic kidney disease.

No	Age	Sex	Dg	Imm. Drugs	No of Drugs	S.m	P. a	C. m
1	72	F	IgAN	CyA	10	+	-	-
2	48	M	IgAN	CyA+MMF	8	+	-	-
3	84	M	IgAN	CyA+MMF	5	+	-	-
4	51	M	IgAN	CyA+MMF	8	-	-	-
5	51	M	IgAN	CyA+MMF	12	-	-	-
6	81	M	PKD	dialysis	17	-	-	+
7	72	F	PKD	CyA+MMF	11	-	-	-
8	78	F	PKD	CyA+MMF	7	-	-	-
9	62	M	DM	MMF+TAC	15	-	-	+
10	60	M	DM	MMF+TAC	10	-	+	-
11	43	M	DM	CyA+MMF	9	-	-	-
12	60	F	DM	MMF+TAC	19	-	-	-
13	52	M	DM	CyA+MMF	9	-	-	-
14	39	M	DM	MMF+TAC	18	-	-	-
15	63	M	DM	MMF+TAC	11	-	-	-
16	64	M	DM	CyA+MMF	14	-	-	-
17	71	F	CIN	CyA+MMF	17	-	-	-
18	39	M	MPO	predialysis	10			

Occurrence of *Stenotrophomonas maltophilia* (S.m), *Pseudomonas aeruginosa* (P.a) *and Chryseobacterium meningosepticum* (C.m). IgAN: IgA Nephropathy; PKD: Polycystic Kidney Disease; DM: Diabetes Mellitus; MPO: MPO Vasculitis; CIN: Chronic Interstitial Nephritis; Imm. Drugs: Immunosuppressive Drugs; CyA: Cyclosporine; MMF: Mycofenolate Mofetil; TAC: Tacrolimus; No of drugs: Number of Total Drugs.

Twelve patients had also been previously examined and treated at the predialysis stage between the years 2000 and 2005, and then followed-up until 2015. Their general health data were combined with oral examination records. The oral examination was made in a normally equipped dental unit at the hospital. The same periodontist (H Ruokonen) examined the patients in both occasions, at predialysis and at follow-up. Patients underwent a full clinical and radiographic oral and periodontal examination. Their medical history was available in hospital records. World Health Organization (WHO) criteria were used in recording the oral health status [14,15]. Periodontal status included recording gingival recessions, periodontal pocket depths (measured from six sites), furcation lesions, visible plaque index, bleeding on probing index, and signs of gingival overgrowth and mucosal lesions. Caries lesions were recorded clinically and from the radiographs. Bite-wing X-rays were taken when needed. Panoramic radiographs of the jaws had been taken from all patients and analyzed by a hospital radiologist specialized in dental and oral radiology. Total Dental Index (TDI, range 0-10), which describes the inflammatory burden caused by oral infection foci (caries, periodontitis, periapical lesions and pericoronitis), was calculated [16]. Periodontal Inflammatory Burden Index (PIBI) describes inflammatory burden related to periodontitis was also calculated [17]. The indices PIBI and TDI are described in Table 1. The basic characteristics of the study subjects are given in Table 2.

Clinical sample analyses

Subgingival dental plaque samples were collected from 18 patient periodontal deep pockets using sterile curettes. The samples were placed immediately into Viability Medium Göteborg Agar (VMGA) media. Before sampling supragingival plaque was removed.

Table 3: Comparison of TDI and PIBI scores and salivary flow rates of patients at the predialysis and post-transplantation stage.

Predialysis	stage (*N*=12) ‡	Post-transplantation stage (*N*=18)	*P*-value#
TDI*†	3.0 (2.0-3.0)	2.0 (0.0-3.0)	**0.028**
PIBI*	6.0 (2.0-13.0)	0.0 (0.0-1.25)	**0.016**
Stimulated salivary flow-rate* (>0.1 ml/min)	1.20 (0.78-1.88)	0.61(0.22-0.91)	**0.025**
Unstimulated salivary flow-rate*(>0.7 ml/min)	0.40 (0.17-0.80)	0.21(0.85-0.63)	**0.031**

‡Six patients were not attended in the predialysis examination
#*P*-values obtained from the Wilcoxon matched-paired signed-rank test * Median distribution with IQR (Interquartile range) values
†TDI value missing from one patient in the predialysis stage, the median obtained from 11 patients

Table 4: Cultivation of VMGA subgingival dental plague samples from 6 patients at the post-transplantation stage with uncommon findings of *S.maltophilia**, *Cryseobacterium meningosepticum*** and *Pseudomonas aeruginosa****.

Bacteria	Patient number					
	1*	2*	3*	6**	9**	10***
A.a	-	-	-	-	-	-
P.gingivalis	0.10%	-	-	4%	-	0.40%
T.forsythia	-	-	-	-	-	-
P.intermedia	-	0.20%	14%	-	-	21%
P.micra	-	-	3%	-	-	1%
C.rectus	1%	-	<0.01 %	-	-	3%
Total amount (CFU)#	7x10exp8	2x10exp8	1x10exp8	3x10exp5	5x10exp7	1x10exp8
Candida	+	-	+	+	+	+

#CFU: Colony Forming Unit.

Two samples were taken from each patient and from the same sites, one for cultivation in the hospital laboratory of periodontal pathogenic bacteria *Aggregatibacter actinomycetemcomitans (Aa)*, *Porphyromonas gingivalis (Pg)*, *Prevotella intermedia (Pi), Tannerella forsythia (Tf)*, *Parvimonas micra (P.m),* and *Campylobacter rectus (C.r)*. Presence of live pseudomonas bacteria in pocket samples was analyzed with selective *Pseudomonas* agar plates (24-48 h at +37°C) supplemented with CFC (cephalothin, fucidin, cetrimide) (Merck Millipore, Billerica, MA, USA). Identification of live bacterial strains were performed with the API20NE method according to the instructions by the manufacturer (BioMerieux, Marcy-l'Étoile, France).

Cotton swabs were used to sample the dorsal surface of the tongue or cheek mucosa for detecting yeasts. The Transpocult© dip-slide method was used for cultivation (Copan Diagnostics Inc., Murrieta, CA, USA). Resting saliva was collected for 5 min using a free-flow method as previously described [18]. Stimulated saliva samples were collected for 5 min by giving the patients a 1 g piece of paraffin to chew. Salivary flow rates were measured as millimeter per minute.

Statistical analyses

Associations of uncommon bacterial findings of pathogens and *Candida* were analyzed by cross-tabulation and chi-square tests. TDI and PIBI were reported by median values with an interquartile range (IQR) and P-values obtained from a Wilcoxon matched-paired signed-rank test. Statistical software program SPSS version 22 was used for analyses (Chicago, Illinois, USA).

Results

The eighteen patients had the following etiology of their CKD: diabetic nephropathy (*N*=8), IgA nephropathy (*N*=5), polycystic kidney disease (*N*=3), interstitial nephritis (*N*=1) and MPO vasculitis (*N*=1). In twelve patients, all oral infection foci had been treated at the predialysis stage in our hospital between the years 2000-2005.

By the follow-up, sixteen patients had received a kidney transplant, one patient was in hemodialysis since the year 2008 (patient #6), and one patient was still at the predialysis stage (patient number 18) (Table 2). All patients were under immunosuppressive treatment with the exception of two cases (patient's number 6 and number 18). In the patient number 18 with MPO vasculitis the immunosuppression had been stopped after previous examination. The immunosuppressive treatment included a calcineurin inhibitor (either cyclosporine A or tacrolimus), an antimetabolite (mofetil mycophenolate [*N*=17] or azathioprine [*N*=1]), and steroids (*N*=1) (Table 2).

At the predialysis stage, the median TDI score was 3 (IQR 2.0 - 3.0) and the median PIBI score was 6 (IQR 2.0 - 13.0). The median scores decreased to 2 (IQR 0.0–3.0) for TDI and to 0 (IQR 0.0–1.25) for PIBI, indicating good oral health at the post-transplantation stage in most of the patients (*P*=0.028 and *P*=0.016) whose oral infection foci had been treated at the predialysis stage. Both stimulated and unstimulated salivary flow-rates decreased at the post-transplantation stage in these patients (*P*= 0.025 and *P*= 0.031) (Table 3).

We further analyzed pooled subgingival plaque samples from the periodontal pockets of 17 patients. In one patient, we were unable to recover enough biological material. The result of the culture was*: Prevotella intermedia* (13/17; 76%) > *Parvimonas micra* (7/17; 41%) >*Porphyromonas gingivalis* (5/17; 29%) >*Campylobacter rectus* (3/17; 18%) >*Tannerella forsythia* (2/17; 12%) >*Aggregatibacter actinomycetemcomitans* (0/17; 0%).

Culture screening of the *Pseudomonas* selective agar plates revealed uncommon bacterial findings in 33% (6/18) of the patients. *S. maltophilia* (Sm) was detected in three patients, *C. meningosepticum* (Cm) in two patients, and *P. aeruginosa* (Pa) in one patient. *Candida* was positive in 44% (8/18) of the patients associating with uncommon bacterial findings in five out of 8 patients, (*P*<0.05). Of the *Candida* species, *C. albicans* was the most commonly detected (*N*=7), while *C. krusei* was found in one patient. All six patients with uncommon

Table 5: Association between uncommon bacterial findings and oral *candida* infection as well as salivary flow rates at the post-transplantation stage.

	No uncommon bacteria*	Uncommon bacteria*	P**
No *Candida* infection (-)	9 (75 %)	1 (16.7 %)	
Candida infection (+)	3 (25 %)	5 (83.3 %)	0.019
Stimulated salivary flow rate†			
0.0 - 0.7 ml/min	7 (58.3 %)	4 (66.7 %)	
0.7 – 2.0 ml/min	5 (41.7 %)	2 (33.3 %)	0.732
Unstimulated salivary flow rate‡			
0.0 - 0.1 ml/min	3 (25 %)	3 (50 %)	
0.1 - 1.1 ml/min	9 (75 %)	3 (50 %)	0.289
Total drugs (median 10.5)			
5- 10.5	5 (41. 7 %)	4 (66.7 %)	
11-19	7 (58.3 %)	2 (33.3 %)	0.317

*Uncommon bacteria findings: *S. maltophilia, C. meningosepticum, P. aerugiosa*
†Hyposalivation cut point for the stimulated salivary flow rate 0.7 ml/min
‡ Hyposalivation cut point for the unstimulated salivary flow rate 0.1 ml/min **P*-value obtained from the Pearson chi-square test.

bacterial findings were dentate but three of them had partial dentures. No association was found between the periodontal bacteria and *S. maltophilia*, *C. meningosepticum, or P. aeruginosa*.

No statistical difference between uncommon bacterial findings and the stimulated or unstimulated salivary flow rate and the total number of daily drugs could be found.

The patients with uncommon bacterial findings are described in more detail below and in Table 4-6.

Patients with *S. maltophilia*

All three patients with *S. maltophilia* (numbers 1, 2 and 3 in Tables 2,4 and 6) had IgA nephropathy diagnosis. After peritoneal dialysis (PD) treatment, they had received kidney transplant 7, 9 and 11 years before the last oral examination. Patient #1 suffered from recurrent Herpes zoster lumbar infection and had previously had four peritonitis episodes during a PD treatment period. Peritonitis had not been caused by oral bacteria but by *Micrococcus* and *Enterobacter clocae*. After transplantation, patient 2 had had one infection caused by *Staphylococcus sp*. Patient #3 had had three infections, caused by *Campylobacter*, *Legionella*, and one infection that could not be specified. Patients 1 and 3 had partial dentures with good condition and had no clinical signs of yeast or bacterial infections. However, both these patients had positive oral culture of *C. albicans* and reduced salivary flow (hyposalivation).

Patients with *C. meningosepticum*

Patient #6 (Tables 2,4 and 6) with C. *meningosepticum* found in subgingival sample had polycystic kidney disease and was in hemodialysis treatment for seven years. He also had severe atherosclerosis and due to poor general health was not considered as a candidate for kidney transplantation. He also had a history of several skin infections. No clinical signs of yeast infection could be found in oral cavity. However, positive culture for *C. albicans* and hyposalivation was detected.

The other patient #9, (Tables 2,4 and 6) with *C. meningosepticum* had been diagnosed with type 2 diabetes. The patient had received a kidney transplant after two years of PD treatment. During this treatment, the patient had had one peritonitis episode and after kidney transplantation severe pneumonia. The patient had removable denture in the upper jaw with good condition and no signs of yeast or bacterial infection. However, he also had hyposalivation. Moreover, *C. albicans* and *C. krusei* were detected.

Table 6: Dental clinical characteristics of *S. maltophilia*`, *C. meningosepticum*\*\*, and *P. aeruginosa*\*\*\* at the post-transplantation stage. Numbers in the first line indicate the patient`s ID in the study.

Clinical index	1*	2*	3*	6**	9**	10***
TDI[#]	3	0	6	4	2	0
PIBI[¤]	1	0	0	0	0	0
VPI%[†]	97.5	4	6.7	12.5	12.5	0.6
No of teeth	3	31	15	15	8	28

[#]TDI is a Total Dental Index, ref. no 16
[¤]PIBI is a Periodontal Inflammatory Burden Index, ref. no 17
†VPI (%): Visible Plaque Index (%) calculated from four sites of every tooth, ref. no 14 and 15.

Patient with *P. aeruginosa*

P. aeruginosa was detected from subgingival sample from patient #10 who had type 1 diabetes (Tables 2,4 and 6). The patient had received a kidney transplant after six years on dialysis, first PD and then hemodialysis. During dialysis treatment, the patient had had seven episodes of peritonitis either with *S. aureus* or cultivation negative. Since 2011, he had also suffered from *P. aeruginosa* infection in the lower limb which was resistant to medication. He had good oral health but had hyposalivation. Culture for *C. albicans* was positive.

Discussion

Overall, chronic kidney disease patients of the present study had fairly good oral health at the post-transplantation stage as shown by the TDI and PIBI scores, and by lack of deep periodontal pockets. This finding was not surprising since all CKD patients in our hospital go through a careful oral examination with subsequent treatment of infections before entering dialysis and before they are put on the list for organ transplantation. In spite of this, however, uncommon bacterial findings were found from the patients, namely *P. aeruginosa* in one, *C. menigosepticum* in two and *S. maltophilia* in three patients. *Candida* was also prevalent and hyposalivation was a common observation. In addition, many patients had cultivable periodontal bacteria: *P. intermedia* in 13/17 patients, *M. micra* in 7/17, *P. gingivalis* in 5/17, *C. rectus* in 3/17, *and T. forsythia* in 2/17. These periodontal bacterial findings were not associated with the uncommon bacteria, however.

P. aeruginosa is a respiratory pathogen found in immunocompromised patients such as patients with cystic fibrosis or HIV infection [1,5]. Before colonizing lungs it may cross different anatomical sites such as the nose, the paranasal sinuses, and the oral cavity. The source is unclear. It has been reported that the patients are initially colonized by a single environmental strain that persists for several years [1,5].

P. aeruginosa with periodontal bacteria *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, *T. forsythia*, *T. denticola*, *P. intermedia*, *E. corrodens*, *C. rectus*, and *P. micra* has previously been detected in subgingival plaque samples and saliva from patients with cystic fibrosis or with periodontal disease pointing to the possible role of oral cavity as reservoir for *P. aeruginosa* [1,19], *P. aeruginosa* has also been found in plaque samples from removable dentures of elderly patients further indicating that oral cavity can harbor it [4]. These reports are in line with findings of the present study. *P. aeruginosa* is resistant to antibiotics and difficult to eradicate as was the case also in our patient who had persistent lower limb infections colonized by *P. aeruginosa* for several years.

S. maltophilia (previously known as *Pseudomonas maltophilia*, *Xanthomonas maltophilia*) is a nosocomial pathogen causing infections in immunocompromised patients. It forms biofilms and is resistant to antibiotics [20]. It has been an etiologic agent of catheter-related infections [21]. Patients with type 1 diabetes have been reported to have higher frequencies of *S. maltophilia* DNA fragments in their sera compared with non-diabetic subjects. In patients with diabetes, levels of serum IgA antibodies against pseudomonas bacteria correlated significantly with the serum, C-reactive protein [22]. *S. maltophilia* was detected in the oral cavity of two of our CKD patients. *S. maltophilia* is an important nosocomial pathogen among immunocompromised patients and it may be life-threatening especially in hospitalized patients [21]. The increase in *S. maltophilia* detection rates may be associated with the changes in antibiotic use and changing nature of hospital patient population in general [23]. Therefore, it is important to prevent colonization of these bacteria and note that it can also be harbored in the mouth.

Chryseobacterium spp. are organisms of low virulence and therefore their presence usually indicates colonization but not infection, except for *C. meningosepticum*, formely known as *Flavobacterium meningosepticum*. This microorganism is known to cause a variety of infections in immunocompromised patients, such as dialysis and kidney transplant patients, or in patients with diabetes, those on immunosuppressive medications, or with neutropenia. Since *C. meningosepticum* is inherently resistant to most antibiotics it can be a potential nosocomial pathogen [24,25].

In our study, the uncommon bacterial findings were associated with positive culture of *Candida* species. *Candida albicans* may be part of the commensal microbial flora, but when the host immune defenses are impaired recurrent infections may occur, as was seen in our study. Hyposalivation increases the risk for *Candida* colonization and patients taking multiple prescribed medications daily have significantly lower stimulated or unstimulated salivary flow rates than those with less daily medications [10,11]. However, in our study where salivary flow rates were seen to be decreased in the post-transplantation stage this was not the case in two patients with uncommon bacterial findings.

Finally, it needs to be pointed out that *P. aeruginosa*, *S. maltophilia,* and *Chryseobacterium spp*. are uncommon pathogens mainly found in immunocompromised patients and that these bacteria cannot be found by routinely used conventional culture methods for periodontal pathogens. This was also the case in the present study.

Conclusion

Our study hypothesis was confirmed since the results showed that CKD patients´ oral cavity indeed harbored both nosocomial and opportunistic pathogens probably due to immunosuppressive treatment or the disease itself. The often encountered concomitant *Candida* infection might also alter the oral microbiota. Furthermore, even though TDI and PIBI indexes were low at the post-transplantation stage indicating good oral health in most of our patients, the present results emphasize the role of the oral cavity as a source of potentially dangerous pathogens in immunocompromised patients thus challenging the oral health care personnel and diagnosis.

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Competing Financial Interests

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References

1. Caldas RR, Le Gall F, Revert K, Rault G, Virmaux M, Gouriou S, et al. Pseudomonas aerugiosa and periodontal pathogens in the oral cavity and lungs in cystic fibrosis patients: a case-control study. J Clin Microbiol. 2015;53(6):1898–907.
2. Scannapieco FA. Pneumonia in nonambulatory patients. The role of oral bacteria and oral hygiene. J Am Dent Assoc. 2006;137:21S-25S.
3. Tada A, Hanada N. Opportunistic respiratory pathogens in the oral cavity of the elderly. FEMS Immunol Med Microbiol. 2010;60(1):1-17.
4. O'Donnell LE, Smith K, Williams C, Nile CJ, Lappin DF, Bradshaw D, et al. Dentures are a Reservoir for Respiratory Pathogens. J Prosthodont. 2016;25(2):99-104.
5. Gale MJ, Maritato MS, Chen YL, Abdulateef SS, Ruiz JE. Pseudomonas aeruginosa causing inflammatory mass of the nasopharynx in an immunocompromised HIV infected patient: A mimic of malignancy. IDCases. 2015;2(2):40–3.
6. Schander K, Jontell M, Johansson P, Nordén G, Hakeberg M, Bratel J. Oral infections and their influence on medical rehabilitation in kidney transplant patients. Swed Dent J. 2009;33(3):97-103.
7. Helenius-Hietala J, Aberg F, Meurman JH, Isoniemi H. Increased infection risk postliver transplant without pretransplant dental treatment. Oral Dis. 2013;19(13):271–8.
8. Simonsen JR, Harjutsalo V, Järvinen A, Kirveskari J, Forsblom C, Groop PH, et al. Bacterial infections in patients with type 1 diabetes: a 14-year follow-up study. BMJ Open Diabetes Res Care. 2015;3(1):e000067.

9. Haririan H, Andrukhov O, Bertl K, Lettner S, Kierstein S, Moritz A, et al. Microbial analysis of subgingival plaque samples compared to that of whole saliva in patients with periodontitis. J Periodontol 2014;85(6):819–28.

10. Närhi TO, Meurman JH, Ainamo A. Xerostomia and hyposalivation: causes, consequences and treatment in the elderly. Drugs Aging. 1999;15(2):103-16.

11. Närhi TO, Meurman JH, Ainamo A, Nevalainen JM, Schmidt-Kaunisaho KG, Siukosaari P, et al. Association between salivary flow rate and the use of systemic medication among 76-, 81-, and 86-year-old inhabitants in Helsinki, Finland. J Dent Res. 1992;71(12):1875-80.

12. Pieralisi N, de Souza Bonfim-Mendonça P, Negri M, Jarros IC, Svidzinski T. Tongue coating frequency and its colonization by yeasts in chronic kidney disease patients. Eur J Clin Microbiol Infect Dis. 2016;35(9):1455–62.

13. Vesterinen M, Ruokonen H, Leivo T, Honkanen AM, Honkanen E, Kari K, et al. Oral health and dental treatment of patients with renal disease. Quintessence Int. 2007;38(3):211-9.

14. World Health Organization 1997. Oral health surveys – basic methods, 4th edn; World Health Organization, Geneva. p.68.

15. Kramer IR, Pindborg JJ, Bezroukov V, Infirri JS. Guide to epidemiology and diagnosis of oral mucosal diseases and conditions. World Health Organization. Community Dent Oral Epidemiol. 1980;8(1):1-26.

16. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjälä SL, et al. Association between dental health and acute myocardial infarction. BMJ. 1989;298(6676):779-81.

17. Lindy O, Suomalainen K, Mäkelä M, Lindy S. Statin use is associated with fewer periodontal lesions: A retrospective study. BMC Oral Health. 2008;8:16.

18. Meurman JH, Rantonen P. Salivary flow rate, buffering capacity, and yeast counts in 187 consecutive adult patients from Kuopio, Finland. Scand J Dent Res. 1994;102(4):229-34.

19. da Silva-Boghossian CM, do Souto RM, Luiz RR, Colombo AP. Association of red complex, A. actinomycetemcomitans and non-oral bacteria with periodontal diseases. Arch Oral Biol. 2011;56(9):899-906.

20. Brooke JS. Stenotrophomonas maltophilia: an emerging global opportunistic pathogen. Clin Microbiol Rev. 2012;25(1):2-41.

21. Araoka H, Baba M, Yoneyama A. Risk factors for mortality among patients with Stenotrophomonas maltophilia bacteremia in Tokyo, Japan, 1996-2009. Eur J Clin Microbiol Infect Dis. 2010;29(5):605–8.

22. Peräneva L, Fogarty CL, Pussinen PJ, Forsblom C, Groop PH, Lehto M. Systemic exposure to Pseudomonal bacteria: a potential link between type 1 diabetes and chronic inflammation. Acta Diabetol. 2013;50(3):351-61.

23. Nyc O, Matejkova J. Stenotrophomonas maltophilia: Significant contemporary hospital pathogen-review. Folia Microbiol (Praha) 2010;55(3):286–94.

24. Dias M, Prashant K, Pai R, Scaria B. Chryseobacterium meningosepticum bacteremia in diabetic nephropathy patient on hemodialysis. Indian J Nephrol. 2010;20(4):203–4.

25. Perera S, Palasuntheram C. Chryseobacterium meningosepticum infections in a dialysis unit. Ceylon Med J. 2004;49(2):57-60.