The relationship between oral diseases and infectious complications in patients under dialysis

Running title:
Oral health and dialysis-related infections

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Authors: Ilona Arenius[1], Hellevi Ruokonen[1], Fernanda Ortiz[2,3], Jussi Furuholm[1], Hannamari Välimaa[4,5], Nagihan Bostanci[6], Maija Eskola[2], Anna Maria Heikkinen[1], Jukka H. Meurman[1], Timo Sorsa[1,6], Karita Nylund[1]

[1] Department of Oral and Maxillofacial Diseases, Helsinki University Hospital and University of Helsinki, Helsinki, Finland.
[2] Department of Medicine, Division of Nephrology, Helsinki University Hospital, Helsinki, Finland.
[3] Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland.
[4] Department of Virology, University of Helsinki, Helsinki, Finland.
[5] Department of Oral and Maxillofacial Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
[6] Section of Periodontology and Dental Prevention, Division of Oral Diseases, Department of Dental Medicine, Karolinska Institutet, Huddinge, Sweden.

Correspondence: Ilona Arenius,
Department of Oral and Maxillofacial Diseases, Head and Neck Center, Helsinki University Hospital
Post address: HUH Head and Neck Center, P.O. Box 220, 00029 HUS, Helsinki, Finland
Email: ilona.arenius@helsinki.fi
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ABSTRACT

Objectives

Association was investigated between oral health before dialysis and the incidence of systemic infections during dialysis. We hypothesized that low-grade systemic

inflammation caused by poor oral health associates with infectious episodes in patients on dialysis, despite earlier eradication of oral infection foci.

Subjects and methods

117 patients (46 with peritoneal and 71 with hemodialysis) were examined and treated at predialysis stage and followed-up during dialysis. Number of infection episodes and microorganisms cultured from blood and peritoneal fluid were analyzed. Number of teeth, Periodontal Inflammatory Burden and Total Dental Index scores were assessed and salivary matrix metalloproteinase 8, triggering receptor on myeloid cells 1, peptidoglycan recognition protein 1 (PGLYRP1), and interleukin-1β were measured.

Results

In hemodialysis, 134 infection episodes were recorded, while peritoneal dialysis group had 77 peritonitis episodes. Culture-negative samples were 69 % in hemodialysis and 23 % in peritoneal dialysis group. Staphylococci were the most frequently associated micro-organisms. Infections during dialysis did neither associate with oral health parameters nor with salivary inflammatory biomarkers, except for PGYLRP1, which associated with number of infection episodes during hemodialysis (p=0.046).

Conclusions

Number of infection episodes during hemodialysis were associated with salivary PGYLRP1 but not the other salivary markers or oral infection markers.

INTRODUCTION

Patients with chronic kidney disease (CKD) on hemodialysis (HD) or peritoneal dialysis (PD) are susceptible to infections associated with high morbidity and mortality. Against matched general population controls, mortality hazard ratios have been reported to be 12.6 for HD patients and 9.2 for PD patients, respectively (Neovius, Jacobson, Eriksson, Elinder, & Hylander, 2014). Infections are common in both HD and PD patients, mainly because the skin barrier iinterrupted during the treatment.

HD patients have higher incidence of bloodstream infections compared with PD patients, accounting for a substantial number of hospitalizations (Patel, Kallen, & Arduino, 2010). HD vascular access device (HVAD) infection rate has been estimated to average 3.5 cases per 100 months (Rojas et al., 2013; Tokars et al., 2001). The most common bacteria isolated from the HD infections are coagulase negative staphylococci (CONS) and *Staphylococcus aureus* (Berman et al., 2004; Tokars et al., 2001).

PD is associated with infection of the peritoneum, with overall reported infection rate being 0.364 per dialysis year (Nessim, Bargman, & Jassal, 2010). In PD patients, peritonitis remains the most common cause for dialysis modality change from PD to HD. Peritonitis is most commonly caused by Gram-positive bacteria which canmigrate from the skin and

colonize the PD catheter from a failure to follow sterile precautions when performing the PD exchanges (Li et al., 2016). *S. epidermidis* and other CONS are common bacteria in PD-associated infections (Liakopoulos et al., 2017).

Periodontal disease has been shown to associate with CKD (Deschamps-Lenhardt, Martin-Cabezas, Hannedouche, & Huck, 2019; Nylund et al., 2018, 2017; Ruokonen et al., 2017) . Combined with the knowledge that bacteremia or soluble bacterial products originating from the mouth can disseminate to distant sites, we set to investigate the association between oral diseases and dialysis-related infections (Bahrani-Mougeot et al., 2008; Lockhart et al., 2008; Lockhart & Durack, 1999; Meurman & Hämäläinen, 2006; Scannapieco, 1998).

To date, there are only few studies on the association between oral bacteria and dialysis infections, with two of such studies focusing on HVAD infections (D'Amato-Palumbo, Kaplan, Feinn, & Lalla, 2013; Shariff et al., 2004). These studies have failed to show a link between oral infections and dialysis-related complications. Both these studies have focused on bacterial analyses but lack the data on the actual oral health condition. A more recent study showed an association between PD-related peritonitis and oral hygiene habits but no connection between PD-related infections and the oral health status had been addressed (Oka et al., 2018).

As treatment of end-stage CKD aims towards kidney transplantation, the current policy in our hospital is to eradicate all possible dental infectious foci prior to commencing dialysis. The aim of the present study was to investigate the association between oral health status before dialysis initiation and the incidence of systemic infections during dialysis. The overall study hypothesis was that long-lasting low-grade systemic inflammatory burden caused by poor oral health associates with infectious episodes in patients on dialysis, even though oral infection foci had been eradicated at predialysis stage.

MATERIALS AND METHODS

Ethical committee of the Helsinki and Uusimaa Hospital District, Finland had approved the study which was conducted according to the principles of the Declaration of Helsinki (Dnro 305/13/03/02/2012).

Study cohort

This is an observational study on 117 patients (70.9% men, 29.1% women; aged 23–83 years) with CKD, followed-up at the Departments of Nephrology and Oral and Maxillofacial Diseases of the Helsinki University Hospital, Helsinki, Finland between the years 2000

and 2015. Details of the baseline examinations have been published earlier (Nylund et al., 2015; Vesterinen, Ruokonen, Furuholm, Honkanen, & Meurman, 2011). In brief, 144 CKD patients were examined and treated at predialysis stage with emphasis on periodontal inflammatory burden. Inclusion criteria were estimated glomerular infiltration rate (eGFR) below 20ml/min, corresponding to advanced CKD stage 4 and 5. We excluded from the analysis of the original cohort 27 patients for the following reasons: 14 died before initiating dialysis, three patients never started dialysis treatment, and 10 patients were lost in follow-up. For dialysis stage, out of the remaining 117 patients, 46 patients were initially settled for peritoneal and 71 patients for hemodialysis. Patients were followed up until kidney transplantation, patient death, or until December 31st, 2015. Six patients changed dialysisode from PD to HD during the follow-up, and there were no switches from HD to PD. During the follow-up, 51 patients deceased. Records pertaining to kidney transplantation and patient mortality have been published earlier (Nylund et al., 2018; Ruokonen et al., 2017). Study design is summarized in figure 1.

Oral examinations and treatment

All patients underwent a full clinical examination by same periodontist (Dr. Hellevi Ruokonen) and a panoramic radiographic examination, as outlined in earlier articles (Nylund et al., 2015; Vesterinen et al., 2011). Following these examinations, a therapeutic eradication of all infectious dental foci was performed, according to the Helsinki University Hospital guidelines. All non–restorable teeth were extracted; these included teeth with abscesses, cysts, severe periodontitis with more than 6 mm periodontal pocket depth after intensive periodontal therapy and marked alveolar bone loss seen in the radiographs, teeth with acute or undisputed chronic periapical disease findings, severely carious teeth where the cavity reached the dental pulp, root remnants, and wisdom teeth with pericoronitis.

The following indices were calculated from the dental records and categorized into two groups by medians: Number of teeth was calculated from the dental records. Total Dental Index (TDI) was calculated from all teeth, taking into account caries, periodontitis, periapical and pericoronitis lesions. The index ranges from 0 to 10 (Mattila et al., 1989). Periodontal inflammatory burden index (PIBI) was calculated from 28 teeth. The PIBI index combines the data on periodontal probing depth and is calculated by adding the number of moderate pockets to the weighted number of periodontal sites indicating advanced periodontitis(Lindy, Suomalainen, Mäkelä, & Lindy, 2008).

Pro-inflammatory biomarkers matrix metalloproteinase (MMP)-8, triggering receptor on myeloid cells 1 soluble form (sTREM-1), peptidoglycan recognition protein 1 (PGLYRP1),

and interleukin (IL)-1β were analyzed from the salivary samples. Salivary sTREM-1, PGLYRP1, and IL-1β were measured by commercially available specific ELISA kits in pre-dialysis stage. Salivary MMP-8 was analyzed by time-resolved immunofluorometric assay (IFMA) using monoclonal MMP-8–specific antibodies as catching and tracing antibodies, respectively. The tracer antibody was labeled with europium-chelate. These baseline methods have been reported earlier (Nylund et al., 2015, 2017).

After appropriate treatment, all patients were set on a personalized re-call schedule to maintain satisfactory oral health during follow-up. However, compliance was not followed when 53 patients (surviving patients as shown in Figure 1) were clinically assessed again at the end of the study period. Our earlier experience from this longitudinal study showed a significant improvement in the patients' clinical oral health parameter when compared to baseline (Nylund et al., 2018).

Systemic infections and microbiological analysis

All infection episodes and results from blood and peritoneal fluid samples during dialysis were retrieved from the hospital records.

We defined infectious episode in HD patients as the occurrence of febrile episode during a hemodialysis session, after excluding other, non-dialysis related infectious foci, such as respiratory tract infection or diabetic foot. A diagnosis of infection was based on the nephrologist's discretion. By our hospital policy, blood samples are always taken for aerobic and anaerobic blood culture in such cases, before antimicrobial treatment is initiated.
In PD-patients admitted to the nephrology ward suspected of peritonitis, PD-effluent samples with more 100 leucocytes/ml along with an appropriate clinical picture lead to antimicrobial treatment and diagnosis of peritonitis. Before antimicrobial therapy initiation, a PD-effluent sample was obtained for culture in aerobic and anaerobic blood culture bottles. Recurrent peritonitis occurring within one month of the previous episode was classified as a single infectious episode.

Blood and peritoneal fluid samples were incubated in blood culture bottles according to standard procedures at Helsinki University Hospital Laboratory (HUSLAB) for a maximum of 5–6 days or until they became positive and the microbes were identified according to standard methods of the laboratory.

Statistical analysis

A software program IBM SPSS Statistics (version 25.0, IBM Corp., Armonk, N.Y., USA) was used for statistical analyses. Chi-square test was conducted for calculating associations

between categorical variables and Spearman's rank-order correlation to assess the relationship between continuous variables. For further analyses the continuous variables were transformed into dichotomous (high vs. low) by their median values and compared with chi-square test. A statistical level of 0.05 was used for statistical significance in all analyses.

RESULTS

HEMODIALYSIS

Infections and microbial findings in HD patients

HD patients were on dialysis for median time of 37 months (mean 47 months) before end of follow-up. Of the 71 HD patients, 44 had at least one or more infectionepisodes; 27 patients had no infections (median was 1, mean 1.89, range 0–14). In this study, the number of any infection during HD was divided into two groups by 0 *vs*. 1 or more infections. Time on dialysis correlated positively with the number of infectious episodes (Spearman's ρ=0.445, p=0.004).

Total number of infection episodes was 134. Of these, two infection episodes were polymicrobial, *i.e.* two bacterial species were discovered in blood culture. 94 infection episodes were culture-negative, with 94 blood culture-negative samples (69.1%). Patients had a total of 42 bacterial findings in blood culture samples within 40 infection episodes. Gram-positive cocci comprised the largest group of bacterial findings, 83.3% of all culture-positive samples. *S. aureus* (47.6%) and CONS (11.9%) were themost common bacterial findings. Table 1 provides listing of all microbial findings.

Oral health parameters and systemic infections in HD patients

No statistically significant associations could be found between the number of systemic infection episodes among the HD patients and scores of PIBI, TDI, or the number of teeth at predialysis stage. TDI could be calculated from only 66 out of 71 HD patients because radiological analyses were not available from all the patients at the time of investigation. There was no statistically significant difference when comparing TDI values and the number of infection episodes (p=0.760). Table 2 provides therespective clinical values.

Predialysis salivary proinflammatory biomarkers and systemic infection episodes in HD patients

Salivary biomarker analysis was available from 54 out of 71 patients and 35 patients of those 54 patients had at least one infection episode. In patients with one or

more infection episodes, 21 patients had significantly higher PGLYRP1 concentrations (77.8%, divided by median) than the group with lower PGLYRP1 concentrations (N=14, 51.9%, p=0.046). Similar trends were observed in the higher median salivary MMP-8, sTREM-1 and IL1β biomarker concentrations in patients with more infections, but the results were not statistically significant. Table 2 provides the mean salivary biomarker concentrations and the respective p values.

PERITONEAL DIALYSIS

Peritoneal infections and microbial findings in PD patients

PD patients were on dialysis for a median time of 23 months (mean 31 months) before end of follow-up. Of the 46 peritoneal dialysis patients, 29 had at least one peritonitis episode while 17 patients had none. PD patients had a total of 77 infection episodes (median 1, mean 1.63, range 0–7). There was no significant correlation between the time on dialysis and the number of peritonitis episodes (Spearman's ρ=0.105, p=0.651).

Thirty-one PD patients had 77 peritonitis episodes. One infection was polymicrobial, with two bacteria identified. In PD patients 18 peritonitis episodes were culture-negative, 23.1% (N=18) of all bacterial cultures. Patients had a total of 60 bacterial findings in blood culture samples. Similarly to HD-group, Gram-positive cocci made up most of the culture-positive samples, that was 75.0% of all culture-positive samples. The most frequent bacterial findings were *S. aureus* (20.0%) and CONS (38.3%).Table 1 provides listing of all microbial findings.

Oral health parameters and peritonitis episodes in PD patients

There was no statistically significant association between the number of peritonitis episodes and PIBI and TDI scores, respectively, nor between the number of teeth in PD group. TDI could be calculated from 38 out of 46 patients since radiological analyses were not available from all the patients at the time of investigation. Table 3provides the respective clinical parameter values.

Predialysis salivary proinflammatory biomarkers and peritonitis

Biomarker analysis was available from 36 out of 46 PD patients. Twenty-two from 36 had one or more peritonitis episodes. These patients had no statistically significant differences regarding salivary MMP-8, PGLYRP1, sTREM-1 or IL-1β levels in relation to the patients without peritonitis episodes. No statistically significant associations were

found with respect to the number of peritonitis episodes in this regard. Table 3 provides the mean salivary biomarker concentrations.

DISCUSSION

In this study, staphylococci comprised the largest group of bacterial findings both in HD and PD patients. As such, these most common bacterial findings did not probably originate from the oral cavity. In HD, the most common bacterial finding was *S. aureus*, while coagulase-negative staphylococci (CONS) were the most common in PD. Time on HD positively correlated with the number of infection episodes, *i.e.* when dialysis time lengthens, the patient becomes more liable to suffer from an infection complication. The same was not found in PD group, however. A significant number of both blood (69.1%) and peritoneal fluid (23.1%) samples remained negative although patients had been diagnosed with infection. Further study into microbial findings should thus be conducted; maybe by using extended culture time as well as sensitive molecular methods such as PCR or next-generation sequencing. This approach would not only facilitate the recovery of bacteria that are difficult to culture (including certain oral bacteria) but would also unveil the as yet uncultured species.

Infection episodes during HD significantly associated with higher salivary levels of PGLYRP1, suggesting that selected salivary biomarkers may indicate ongoing systemic infection in dialysis patients. Although the main, phyiological functions of PGLYRP1 are still ambiguous, PGLYRP1 can be induced in response to systemic infection (Osanai et al., 2011). Recent work by Silbereisen et al. demonstrated that the levels of PGLYRP-1 were upregulated in saliva in response to experimental dental plaque accumulation (Silbereisen et al., 2019). Although PGLYRP1 has antibacterial activities against gram-positive bacteria, the linking of salivary or serum PGYLRP1 to systemic infection episodes during HD was not previously demonstrated (Lu et al., 2006; Wang et al., 2007). Potential correlations between serum and salivary levels of PGLYRP1 in HD patients with infection should be further investigated.

Bacteremia episodes or peritoneal infections in dialysis patients were not significantly influenced by TDI, PIBI, number of teeth or salivary inflammatory parameters MMP-8, IL-1β, and TREM-1 measured at pre-dialysis stage. A study by Lahdentausta et al. recently found that while selected salivary biomarkers aided in diagnosis of periodontitis, they did not reflect systemic status in acute coronary syndrome patients. Simultaneous serum samples reflected the systemic status, but not the periodontal condition (Lahdentausta et al., 2018). This result could explain also our results in this regard; salivary biomarkers correlate

selectively with oral health status, while similar biomarkers obtained from serum could reflect systemic inflammation. Nonetheless, studies have shown that calibrated salivary diagnostic tools can be used as prediabetes/diabetes screening (Grigoriadis et al., 2019; Rathnayake et al., 2013). The recent development of oral fluid, *i.e.,* mouthrinse aMMP-8 chair-side/point-of-care, diagnostic technology enables the timing and targeting of preventive therapeutic interventions against oral infections and related inflammation (Grigoriadis et al., 2019; Leppilahti et al., 2018; Sorsa, Gieselmann, Arweiler, & Hernández, 2017). More studies are required also in this regard.

In the present study, infection episodes during peritoneal or hemodialysis were not significantly associated with oral diseases or salivary inflammatory markers, except for PGLYRP1, suggesting that oral condition may not associated with the incidence of infections during dialysis. The fact that before commencing dialysis dental treatment had been given to the patients may bias this result. However, giving dental treatment was a necessity, as kidney transplant timing cannot always be anticipated. Hence, further studies with different protocols are called for in this area.

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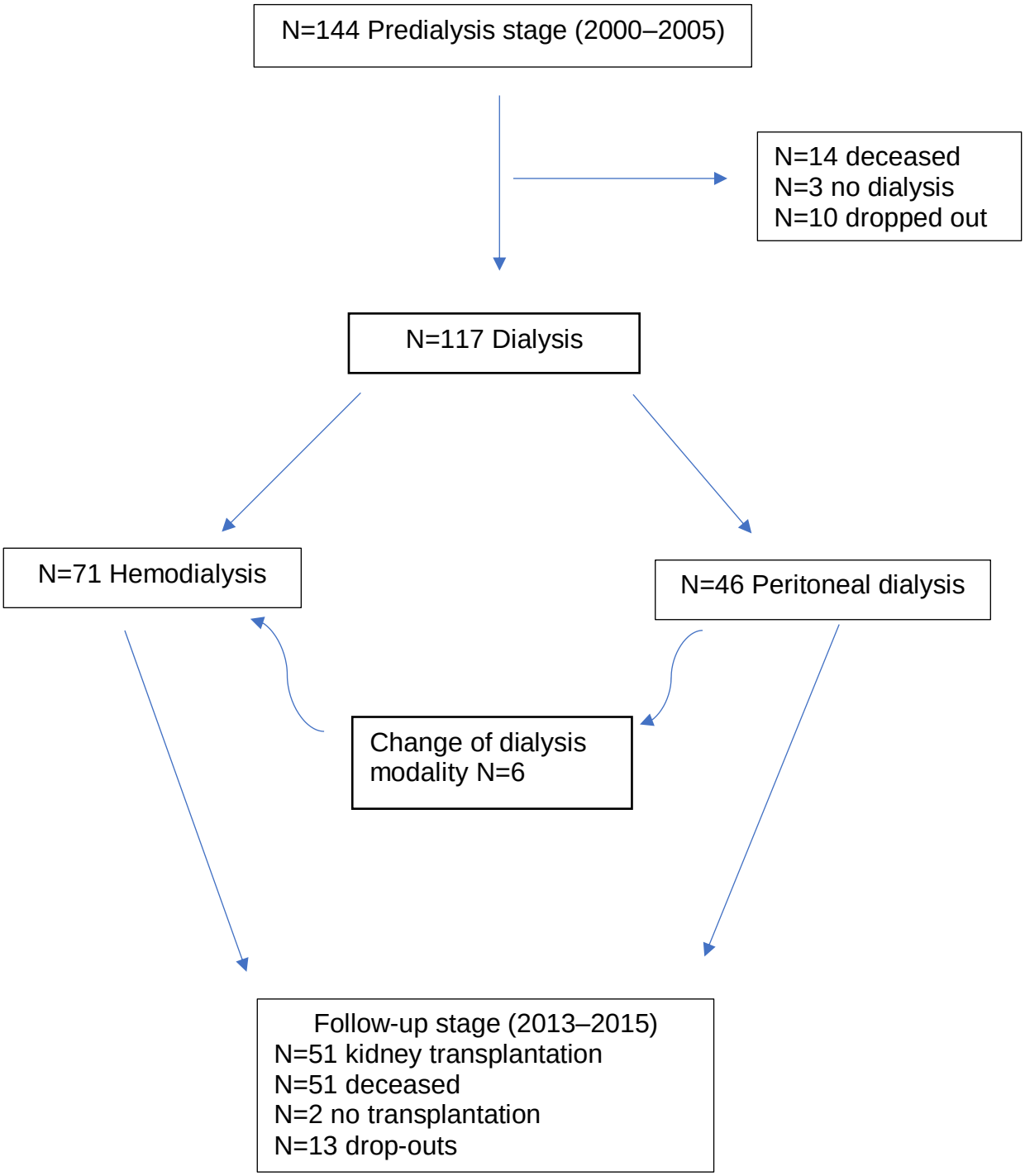
FIGURES

Figure 1. Study Design



TABLES

Table 1. Micro-organisms detected in blood and peritoneal fluid culture results in dialysis patients.

Hemodialysis, N=42	Number (%)	Peritoneal dialysis, N=60	Number (%)
Staphylococcus aureus	20 (47.6)	Coagulase negative staphylococci (CONS) **	23 (38.3)
Coagulase negative staphylococci (CONS)*	6 (14.3)	*Staphylococcus aureus*	12 (20.0)
Enterococcus faecalis	3 (7.1)	*Streptococcus viridans*	6 (10.0)
Corynebacterium jeikeium	3 (7.1)	Diphteroids	4 (6.7)
Beta-hemolytic streptococci	3 (7.1)	*Acinetobacter spp.*	3 (5.0)
Escherichia coli	2 (4.8)	*Enterococcus faecalis*	3 (5.0)
Pseudomonas aeruginosa	1 (2.4)	*Haemophilus*-like gram-negative rod	2 (3.3)
Pseudomonas-like gram-negative rod	1 (2.4)	*Candida albicans*	2 (3.3)
Listeria monocytogenes	1 (2.4)	*Candida parapsilopsis*	1 (1.7)
Gemella sp.	1 (2.4)	*Enterobacter cloacae*	1 (1.7)
Diphteroids (excl. *C. jeikeium*)	1 (2.4)	*Pseudomonas*-like gram-negative rod	1 (1.7)
		Bacillus cereus	1 (1.7)
		Micrococcus luteus	1 (1.7)

*5/6 of the isolates *St. epidermidis*
**12/23 of the isolates *St. epidermidis*

Table 2. Findings in hemodialysis group

	Hemodialysis, N=71, all patients				
			No infections, N=27	1 or more infection episodes, N=44	p-value
Median age, years (range)	55 (26–80)		54	55	0.649
Sex, N (%)					0.110
Female	21 (30%)		5 (19%)	16 (36%)	
Male	50 (70%)		22 (81%)	28 (64%)	
Deceased, N (%)	35 (49.3%)		8 (30%)	27 (61%)	**0.009**
	Median (IQR*)				
Number of teeth	25 (16–27)		25 (22–27)	23 (11–27)	0.550
TDI	3 (2–5)		3 (2–4)	3.5 (2–5)	0.760
PIBI	6 (2–15)		6 (2–15)	5 (1–15)	0.522
	Median pg/mL (IQR*)				
MMP-8	148 (70–203)		112 (70–179)	150 (63–212)	0.393
PGLYRP1	5825 (2800–10532)		4361 (2264–6632)	8117 (3109–11463)	**0.046**
sTREM-1	179 (86–282)		174 (113–274)	185 (51–317)	0.393
IL-1β	82 (43–140)		72 (52–123)	88 (39–162)	0.393

*IQR=interquartile range, lower quartile to upper quartile

Table 3. Findings in peritoneal dialysis group

	Peritoneal dialysis N=46, all patients				
			No peritonitis, N=17	1 or more peritonitis episodes, N=29	p-value
Median age, years (range)	51 (23–83)		48	52	0.359
Sex, N (%)					0.894
Female	13 (28%)		5 (29%)	8 (28%)	
Male	33 (72%)		12 (71%)	21 (72%)	
Deceased, N (%)	16 (35%)		6 (35%)	10 (34%)	0.956
	Median (IQR*)				
Number of teeth	27 (21–29)		26 (23–29)	27 (20–28)	0.127
TDI	3 (2–4)		3 (2–5)	3(3–4)	0.927
PIBI	5 (2–22)		5 (2–33)	5 (2–14)	0.489
	Median pg/mL (IQR*)				
MMP-8	130 (16–191)		161 (108–188)	78 (14–194)	0.494
PGLYRP1	6572 (2815–13918)		6518 (3028–13991)	6453 (2344–13782)	0.060
sTREM-1	193 (65–383)		260 (87–411)	183 (33–329)	0.238
IL-1β	74 (30–142)		74 (47–155)	22 (24–154)	0.060

*IQR=interquartile range, lower quartile to upper quartile