The association between dialysis modality and the risk for dialysis technique and non-dialysis technique-related infections

Anouk T.N. van Diepen^{1,2}, Tiny Hoekstra², Joris I. Rotmans³, Mark G.J. de Boer⁴, Saskia le Cessie^{2,5}, Marit M. Suttorp², Dirk G. Struijk^{1,6}, Els W. Boeschoten⁷, Raymond T. Krediet¹ and Friedo W. Dekker²

¹Division of Nephrology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, ²Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, ³Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands, ⁴Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands, ⁵Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands, ⁶Dianet, Amsterdam-Utrecht, The Netherlands and ⁷Hans Mak Institute, Naarden, The Netherlands

Correspondence and offprint requests to: Anouk T.N. van Diepen; E-mail: a.t.vandiepen@amc.uva.nl

ABSTRACT

Background. Infections are a major cause of morbidity and mortality among dialysis patients. Dialysis modality has been hypothesized to be a potential immunomodulatory factor. The objective of this study was to determine the influence of the first dialysis modality on the risk for infections on dialysis.

Methods. Our study was conducted utilizing the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) cohort of incident dialysis patients. Medical records of all patients from two tertiary care university hospitals and three regional hospitals were reviewed using pre-specified criteria. Information about infections was collected from the start of dialysis until death, modality switch, study withdrawal, kidney transplantation or at the end of the study. Age-standardized incidence rates for infections were calculated. Poisson regression analysis was used to calculate adjusted incidence rate ratios (IRRs).

Results. In total, 452 patients, of whom 285 started with haemodialysis (HD) and 167 with peritoneal dialysis (PD), were included. The median follow-up time on the first dialysis modality was similar for HD and PD, 1.8 and 2.0 dialysis years, respectively. During the first 6 months, the age-standardized infection incidence rate was higher on HD compared with PD patients (P = 0.02). Overall, PD patients had a higher infection risk [adjusted IRR: 1.65, 95% confidence interval (CI): 1.34–2.03], which could be attributed to a 4-fold increased risk for dialysis technique-related infections. The risk for non-dialysis technique-related infections was lower in PD patients (adjusted IRR: 0.56, 95% CI: 0.40–0.79). **Conclusions.** Overall, PD patients carry a higher risk for infections. Interestingly, the risk for non-dialysis technique-related infections was higher in HD patients. The links between dialysis modality and the immune system are expected to explain this difference, but future studies are needed to test these assumptions.

Keywords: epidemiology, haemodialysis, immunology, infection, peritoneal dialysis

INTRODUCTION

Infectious complications among both haemodialysis (HD) and peritoneal dialysis (PD) patients are a major cause of morbidity and hospitalization [1-7] and are the leading non-cardiovascular cause of death [8]. A few studies have compared HD and PD and the risk for infection-related hospitalization and reported contradicting results [2-5, 7]. In these studies, the incidence of infection-related hospitalizations among HD patients ranged between 0.29 and 1.39 per dialysis year, whereas in PD patients, incidence rates between 0.42 and 1.38 per dialysis year were observed. In some studies, an elevated infection risk in PD patients was observed [2, 7], which could predominantly be explained by peritonitis, while others revealed a higher risk for infection in HD patients [3]. However, the majority of studies [3-5, 7] only reported infections leading to hospitalization and did not evaluate whether dialysis modality altered the risk for less severe infections. Thus, an association between dialysis modality and the risk for overall infectious complications has not been well established. Furthermore, it

full reviewing process. Discrepancies were resolved by a third party (R.T.K.). Demographic data collected at the start of dialysis included dialysis modality, age, sex, diabetes and other comorbidities, ethnicity, educational level, smoking, dialysis preparation in an outpatient setting, primary kidney disease grouped into four categories [15], body mass index (BMI), Kahn comorbidity score, medication, C-reactive protein (CRP), haemoglobin and serum albumin. The Kahn comorbidity score [16] is calculated based on a combination of age and the number of comorbid conditions. Patients are classified into low, medium and severe mortality risk. The Kahn comorbidity score has been validated in the NECOSAD cohort [17, 18] and was found to perform equally appropriate when compared with Davis and

Infection definitions

Charlson comorbidity indices.

In general, infection is defined as a host response to invading microorganisms. The presence of microorganisms without a host response is no evidence of infection. In contrast, an inflammatory response is not necessarily a presentation of infectious invasion, but may also result from other pro-inflammatory stimuli [19-21]. Therefore, scoring criteria for infections was strictly pre-specified to secure good-quality data collection. An infection was considered present when (i) diagnosed by a nephrologist or other physician and (ii) supported by evidence such as a positive culture, radiological confirmation or antibiotic, antiviral or antifungal treatment. The diagnosis was required to be accompanied by treatment in the case of a soft tissue infection, a respiratory tract infection other than pneumonia and urinary tract infections. All infections were categorized as summarized in Table 1. Infections were classified as dialysis technique-related infections and non-dialysis technique-related infections. The International Society for Peritoneal Dialysis guidelines/recommendations [22] were used to define recurrent, relapsing and repeating infectious episodes. Both recurrent and repeating, but not relapsing, infectious episodes were scored as a new infection.

bias. The reviewers worked in close collaboration during the

Statistical analysis

Differences in baseline characteristics were tested with an unpaired Student's t-test, Mann-Whitney (continuous data) or χ^2 test (categorical data). Incidence rates are expressed as infections per dialysis year. To adjust for age differences between PD and HD patients, weights derived from the age distribution of

Dialysis technique-related infection Access infections Vascular access-associated sepsis	
Peritonitis	
Non-dialysis technique-related infection	
Cardiac infections	
Gastrointestinal infections	
Respiratory infection	
Non-vascular access-associated sepsis	
Soft tissue infections	
Urinary tract infection	

has not been made evident whether the incidence rate of infections is constant over time, highest directly after the start of renal replacement therapy or increases with time on dialysis.

As expected, dialysis technique-related infections, like peritonitis and vascular access-associated sepsis, were found to be modality-associated [2, 4, 5, 7]. Remarkably, these studies also showed a higher incidence rate of pneumonia in HD patients. A likely explanation is that HD patients are often older and suffer from more comorbidity than PD patients. However, an increased risk for pneumonia remained present after adjustment for these confounding factors [7]. Alternative explanations may be that initiation of HD, compared with PD, is associated with distinct immunological alterations or different environmental exposure [9-14]. These factors may lead to an altered risk profile for non-dialysis technique-related infections.

The aim of the present study was to elucidate the association between dialysis modality and infectious complications. The study was designed to investigate the influence of the first dialysis modality on the risk for overall infectious complications, dialysis technique- and non-dialysis technique-related infections. In addition, the risk for infectious complications over time on the first dialysis modality was compared. We hypothesized that PD patients develop more infections on dialysis, whereas HD patients carry a higher risk for infection directly after the start of dialysis.

MATERIALS AND METHODS

Study design

The present study was conducted in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study cohort. NECOSAD is a multicentre prospective cohort study of dialysis patients from 38 centres in the Netherlands. Incident end-stage renal disease patients, aged ≥18 years, starting dialysis between 1 January 1997 and 1 January 2007 were eligible for inclusion. Medical ethics committees of all participating hospitals approved the study. All participants gave their written informed consent. For the present study, we conducted a review of both in- and outpatient medical records of all patients from five dialysis centres who participated in NECOSAD: two tertiary care university hospitals and there regional hospitals. No exclusion criteria were applied. The dialysis centres were chosen for practical reasons (travel distance and the number of included patients) to assure efficient data collection. Patients were censored at modality switch, withdrawal from the study, transfer to a nonparticipating dialysis centre, kidney transplantation, death or at the end of the study follow-up period in June 2009.

Data collection

Data on infectious complications were retrospectively collected using strictly pre-specified criteria (described below). Information about the incidence and microbiology of infections was collected from the start of renal replacement therapy until death or censoring. Data collection was conducted by two reviewers (A.T.N.v.D. and M.M.S.). To ensure good-quality data collection, the reviewers applied strictly pre-specified criteria, which were developed to minimize the risk of reviewer

the complete study population were used for direct standardization [23]. Age-standardized infection incidence rates were calculated in time intervals after the start of dialysis. Adjusted Poisson regression models with robust standard errors were used to assess the association between the first dialysis modality and the risk for overall infections and specific types of infections. Crude and adjusted incidence rate ratios (IRRs) were calculated to estimate both the overall infection risk and the risk for infectious complications over time. Adjustments were made for baseline measurements of age, sex, diabetes, ethnicity, BMI, primary kidney disease, Kahn comorbidity score, malignancy, chronic pulmonary disease, educational level, smoking and dialysis preparation in an outpatient setting. To assess the influence of HD vascular access on the incidence rate of dialysis technique-related infections among HD patients, we used data collected by previous chart review [24] and calculated the adjusted IRR for dialysis technique-related infections in patients with an arteriovenous graft or fistula at 3 months compared with those with a central venous catheter. A likelihood-ratio test was performed to determine whether the effect of dialysis modality on the risk for infectious complications changed with the time spent on dialysis. The statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics 20) and STATA (Stata/IC 12.1).

Sensitivity analysis

ORIGINAL ARTICLE

To explore a possible bias introduced by acute patients starting renal replacement therapy without proper preparation, analyses were repeated after excluding patients followed <90 days after the start of dialysis. To assess the influence of a potential survival benefit for PD patients (competing risk of death) on the estimates for infection, we carried out a Fine and Gray's proportional subhazards model to calculate the adjusted subhazard ratio in PD, compared with HD, patients. Also, because hospitalization is a marker of disease severity, a sensitivity analysis was performed to explore the association with dialysis modality when only infection-related hospitalizations were taken into account. Furthermore, a Cox proportional hazard model, adjusted for baseline measurements of age, sex, diabetes, ethnicity, BMI, primary kidney disease, Kahn comorbidity score, malignancy, chronic pulmonary disease, educational level, smoking and dialysis preparation in an outpatient setting, was used to evaluate whether the results would change when only the first infection was taken into account. To assess the potential influence of censoring at modality switch on the association between the first dialysis modality and infectious complications, a Cox proportional hazard model using dialysis modality as a time-dependent variable was performed. To evaluate the impact of immunosuppressive therapy on the risk estimates, analyses were repeated after exclusion of patients using immunosuppressive therapy.

RESULTS

Population characteristics

Medical records of 471 NECOSAD patients were reviewed. After excluding patients with incomplete or lost files (n = 19),

a total of 452 patients could be included. The baseline characteristics of the study population are summarized in Table 2. In total, 285 (63%) started with HD and 167 (37%) with PD as their first modality of renal replacement therapy. At the start of dialysis, patients on HD were older, more often Caucasian, had a higher Kahn comorbidity score and a lower haemoglobin level compared with PD patients. The median follow-up time on the first dialysis modality was 1.8 years [interguartile range (IQR): 0.6-3.7] on HD and 2.0 years (IQR: 0.8-3.5) on PD (P = 0.76), with a maximum of 11.3 years. During followup, 35 (12%) HD patients were censored due to a switch to PD, whereas 58 (35%) PD patients were censored due to a switch to HD. Less than 2% of the data on confounding factors were missing. When compared with the complete NECOSAD study cohort, the patients included in this study had similar baseline characteristics (data not shown).

Infection incidence rates

During follow-up, patients on HD experienced 448 infections (0.65/patient/dialysis year) and patients on PD suffered from 355 infections (0.91/patient/dialysis year) on the first dialysis modality. Infection incidence rates over time, standardized for age and stratified by dialysis modality are shown in Figure 1. Within the first 6 months after the start of dialysis, HD patients had a significantly higher age-standardized incidence rate of infectious complications compared with PD patients: 1.72 infections/dialysis year [95% confidence interval (CI): 1.62–1.81] compared with 1.40 infections/dialysis year (95% CI 1.21–1.58) (P = 0.02). After 6 months, the age-standardized incidence rate of infections was higher in PD patients

Table 2. Baseline characteristics of the study population

Characteristics	HD	PD	P-value
Patients (<i>n</i>)	285	167	
Age start dialysis [median (range)]	69.0 (19-88)	54.6 (19-80)	< 0.001
Male (%)	66	63	0.51
BMI [kg/m ² , (mean (SD)]	25.5 (4.2)	25.2 (3.9)	0.54
Ethnicity (% Caucasian)	95	83	0.04
Diabetes (%)	23	17	0.13
Cause of ESRD (%)			
Renovascular disease	24	10	0.29
Diabetic nephropathy	16	12	
Glomerulonephritis	13	20	
Other	47	58	
Kahn comorbidity score	36	21	< 0.001
(% category 3)			
Smoking (%)			
Present	21	31	0.14
Past	49	39	
Never	30	30	
CRP ^a [mg/L; median (IQR)]	6 (3-16)	4 (3-9)	0.01
Haemoglobin ^a [g/dL; mean (SD)]	10.9 (1.4)	11.7 (1.6)	< 0.001
Serum albumin ^a [g/dL; mean	3.21 (0.8)	3.25 (0.8)	0.78
(SD)]			
HD vascular access (% CVC) ^a	11	N/A	N/A
Dialysis preparation in an	68	92	< 0.001
outpatient setting (%)			

BMI, body mass index; ESRD, end-stage renal disease; CRP, C-reactive protein; CVC, central venous catheter; N/A, not applicable; SD, standard deviation; IQR, interquartile range.

^aLevels or % after 3 months on dialysis.

compared with HD patients. During the complete follow-up period, the incidence rate of non-dialysis technique-related infections was higher in HD patients, whereas that of dialysis technique-related infections was higher in PD patients.

Association between dialysis modality and overall infectious complications

Crude and adjusted IRRs are presented in Table 3. The risk for infectious complications was significantly higher in PD patients compared with HD patients, with an adjusted IRR of 1.65. This higher risk can be attributed to the increased risk for PD patients to develop dialysis technique-related infections, like peritonitis and access infection, with an adjusted IRR of 4.10. However, HD patients with a fistula at 3 months had a lower risk for dialysis technique-related infections (adjusted IRR: 0.28; 95% CI: 0.14–0.55) compared with those with a catheter, while an arteriovenous graft resulted in a similar infection risk (adjusted IRR: 0.96, 95% CI: 0.45–2.05). The overall risk for non-dialysis technique-related infection was lower in PD patients compared with HD patients with an adjusted IRR of 0.56. The latter could be explained by a higher risk for non-vascular access-associated sepsis (adjusted IRR: 0.24) and respiratory infections (adjusted IRR: 0.58) in HD patients.

Association between dialysis modality and infection risk over time

The adjusted IRRs over time are reported in Table 4. Directly after the start of dialysis, the overall infection risk was somewhat lower in PD patients with an adjusted IRR of 0.87, although not significant. The incidence rate of infections in HD patients decreased substantially after 3 months, whereas that of infections in PD patients remained stable (Figure 1). Therefore, after 6 months, the adjusted IRRs were significantly higher for PD patients and differences became larger over time. For the interaction between time on dialysis and dialysis modality, the complete follow-up time on the first dialysis modality was taken into account. The time after the start of dialysis, divided into intervals of 6 months, modified the

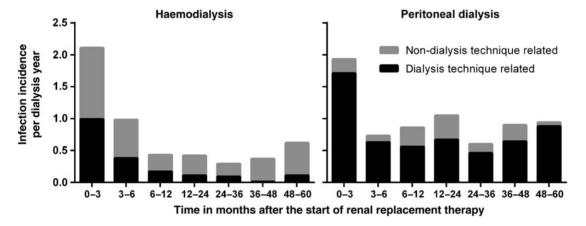


FIGURE 1: Age-standardized dialysis technique- and non-dialysis technique-related infection incidences per dialysis year over time. More detailed information about specific types of infections over time can be found in an online supplemental figure.

Table 3.	Incidence rates and	(adjusted)	IRRs of infectious	complications ^a
----------	---------------------	------------	---------------------------	----------------------------

	Incidence rates per 1000 dialysis years		Crude IRR	Adjusted IRR ^b	Adjusted IRR ^c
	HD	PD			
Total infection	653	914	1.29 (1.08-1.53)	1.31 (1.09–1.57)	1.65 (1.34-2.03)
Dialysis technique-related infection	212	731	3.25 (2.57-4.11)	2.94 (2.28-3.78)	4.10 (3.06-5.58)
Access infection	137	368	2.55 (1.95-3.35)	2.05 (1.54-2.73)	2.84 (2.00-3.98)
Peritonitis	19	358	21.29 (11.17-40.58)	22.57 (11.38-44.78)	28.13 (13.56-58.38)
Vascular access-associated sepsis	56	5	0.09 (0.02-0.36)	0.09 (0.02-0.40)	0.13 (0.03-0.61)
Non-dialysis technique-related infection	441	183	0.40 (0.29-0.53)	0.47 (0.34-0.64)	0.56 (0.40-0.79)
Non-vascular access-associated sepsis	118	21	0.17 (0.08-0.36)	0.17 (0.08-0.35)	0.24 (0.11-0.52)
Cardiac	16	0	N/A	N/A	N/A
Gastrointestinal	38	41	1.09 (0.57-2.08)	1.13 (0.54-2.34)	1.05 (0.44-2.35)
Respiratory	152	54	0.34 (0.20-0.57)	0.47 (0.25-0.80)	0.58 (0.31-1.01)
Soft tissue	21	5	0.12 (0.02-0.92)	0.13 (0.01-1.29)	0.15 (0.02-1.46)
Urinary tract	96	62	0.60 (0.36-1.00)	0.71 (0.42–1.19)	0.74 (0.43-1.28)

N/A, incidence rate ratio not available.

^aHD is the reference category.

^bIncidence rate ratio adjusted for age, sex and diabetes.

^cIncidence rate ratio adjusted for BMI, Kahn comorbidity score, primary kidney disease, ethnicity, malignancy, chronic pulmonary disease, educational level, smoking and dialysis preparation in an outpatient setting.

Table 4. Adjusted incidence rate ratios^a for infection on the first dialysis modality^b over time

	0–3 months (<i>n</i> = 452)	3–6 months (<i>n</i> = 400)	6–12 months (<i>n</i> = 363)	12–24 months (<i>n</i> = 305)	24–36 months (<i>n</i> = 207)
Total infection	0.87 (0.62-1.23)	1.22 (0.69-2.16)	1.66 (1.05-2.62)	2.74 (1.77-4.26)	3.21 (1.51-6.87)
Dialysis technique-related infection	1.96 (1.25-3.06)	3.18 (1.60-6.31)	3.28 (1.77-6.09)	6.56 (3.25-13.22)	19.34 (5.20-71.93)
Non-dialysis technique-related	0.12 (0.05-0.32)	0.29 (0.09-0.97)	0.68 (0.32-1.45)	1.38 (0.79-2.43)	0.71 (0.13-3.74)
infection					

^aIncidence rate ratios adjusted for age, sex and diabetes, BMI, Kahn co-morbidity score, primary kidney disease, ethnicity, malignancy, chronic pulmonary disease, educational level, smoking and dialysis preparation in an outpatient setting.

^bHD is the reference category.

association between the first dialysis modality and the risk for infections (likelihood-ratio test, P < 0.001).

Sensitivity analyses

Similar results were observed when patients followed <90 days after the start of dialysis (n = 50) were excluded from the analysis, which emphasizes that our sample of the NECOSAD cohort included stable incident dialysis patients. Of all patients, 38 died before experiencing an infection. Of these, 32 were treated with HD and 6 with PD. When the adjusted subhazard ratio with death as a competing risk was calculated, the adjusted IRR was somewhat attenuated for overall infection (1.42; 95% CI: 1.08-1.88). Of all infections, 338 (75%) on HD and 179 (50%) on PD were treated in the hospital. When only infection-related hospitalizations were taken into account, the adjusted IRRs for overall infection (1.21; 95% CI: 0.96-1.53) and dialysis technique-related infection (2.9; 95% CI: 2.09-4.19) were somewhat attenuated, whereas the IRR for nondialysis technique-related infection (0.52; 95% CI: 0.34-0.75) did not change. In an unadjusted (HR: 1.36; 95% CI: 1.08-1.71) and adjusted Cox proportional hazard analysis (adjusted HR: 1.54; 95% CI: 1.18-2.02), the association between dialysis modality and infectious complications did not change substantially when only the first infection was taken into account. When a Cox proportional hazard model using dialysis modality as a time-dependent variable was performed the unadjusted (HR: 2.06; 95% CI: 1.48-2.88) and adjusted association (adjusted HR: 2.23; 95% CI: 1.53-3.25) between dialysis modality and infection was somewhat stronger. When patients who received immunosuppressive therapy (PD: n = 7; HD: n = 21) were excluded from the analyses, estimated effects did not change (data not shown).

DISCUSSION

ORIGINAL ARTICLE

This cohort study of incident dialysis patients shows that PD patients are overall at a higher risk for infectious complications compared with HD patients. However, PD was associated with a lower risk for non-dialysis technique-related infections. This association was strongest within the first 6 months after the start of dialysis. After 6 months, the IRRs are not significant without any consistent trend. In both HD and PD patients, the infection incidence rate was highest 0–3 months after the initiation of dialysis and decreased later on. In the first 6 months of dialysis, HD patients had a higher age-standardized incidence rate of infections compared with PD patients, although

this did not remain significant after further adjustment for confounding factors.

Our study has several strengths and weaknesses. Although the NECOSAD data were collected prospectively, we retrospectively collected data on infectious complications. A disadvantage of retrospective data collection is its dependency on accurate record keeping. However, we are confident that a thorough review of the complete original medical records of 452 NECOSAD patients was performed. Most likely, infections of less severity may have been underreported, because they were not recorded or were treated by the general practitioner instead of the nephrologist. We attempted to limit this information bias by reviewing both in- and outpatient files, which allowed us to focus on infectious hospitalizations and infections of less severity treated by the nephrologist. Still, misclassification is probably differential for infections of less severity because PD patients are more likely to consult their general practitioner due to their home-based treatment. It is possible that this may have affected both infection rates and the comparison between modalities.

A major strength of the NECOSAD cohort is that it included a population of stable incident dialysis patients with a long follow-up period. In addition, we were able to follow patients from the start of renal replacement therapy, which was advantageous compared with the majority of previous studies that often excluded the first 90 days on dialysis, which is a high-risk period for infections. No protocol changes or care bundle approaches were introduced during the NECOSAD study period that might have influenced the infection rates over time.

Our study has shown a 1.7-fold higher risk for infectious complications in PD patients. This is consistent with earlier findings in the US Renal Data System database [6] and the Canada Organ Replacement Register [7], although these studies only included infection-related hospitalizations and did not assess less severe infections. In other studies [3-5], no association between dialysis modality and overall infection-related hospitalization rates was observed, although a similar, but not significant trend towards a higher incidence rate on PD could be recognized [4, 5]. A study from Pittsburgh, USA [2], has shown no association between dialysis modality and overall infection rates. In the present study, the association with dialysis modality attenuated when only infection-related hospitalizations were taken into account towards a 1.2-fold higher risk for infection in PD patients, which was no longer significant. This may indicate that PD patients experienced more infections of less severity that did not require hospitalization compared with HD patients.

This study has shown that the increased risk for infectious complications in PD patients could be explained by a 4-fold higher risk for dialysis technique-related infections in PD compared with HD patients, like peritonitis and access infection. The risk for dialysis technique-related infections attenuated towards a 3-fold higher risk, when only infection-related hospitalizations were taken into account. Lafrance *et al.* [7] have shown a similar adjusted hazard ratio of 3.5 for dialysis-related infections in a Canadian cohort.

Interestingly, a 2-fold lower adjusted IRR for non-dialysis technique-related infections was observed in PD compared with HD patients, which did not change when the analysis was limited to infections treated in the hospital. Similar to others [2, 4, 6, 7], we have shown that the incidence rates of respiratory infection and septicaemia are higher in HD patients. Although a well-substantiated pathophysiological explanation has not been elucidated, a number of hypotheses can be considered. The most straightforward hypothesis is that the association might be explained by a difference in underlying health status between HD and PD patients. Consistent with general clinical experience, HD patients were older and carried more comorbidities than PD patients. Although extensive adjustment for confounders was performed, residual confounding, in terms of confounding by indication, cannot be excluded due to the observational design of the study.

Some studies [12–14] suggested that the difference in the incidence rate of pneumonia might be explained by the fact that HD patients are treated predominantly in a hospital setting while PD is a home-based treatment. If so, a high number of typically hospital-acquired microorganisms would be observed causing non-dialysis technique-related infections. However, this was not the case (data not shown).

A pathophysiological explanation of the observed differences between infection rates would be that some characteristics of the dialysis modalities influence the immune system and therefore alter the risk for infectious complications. Fluid overload, accumulation of uraemic toxins and a constant exposure to oxidative stress could have immunosuppressive effects [9]. These effects might be enhanced in HD compared with PD patients, because HD patients are dialysed in an intermittent fashion, wheras PD results in a more continuous removal of fluid and uraemic toxins. Furthermore, it has been suggested that chronic systemic inflammation might alter the function of the immune system [9, 25]. Systemic inflammation in HD patients is induced by the contact of blood with bioincompatible dialysis membranes and accumulation of uraemic toxins. However, in PD, inflammation can be induced by the bio-incompatible dialysate containing glucose and its degradation products [26]. The presence of a better residual renal function in PD patients might temporarily prevent the induction of inflammation [27, 28]. For these reasons, several authors [29, 30] have speculated that the burden of systemic inflammation might be higher in HD patients compared with PD patients. The observation that HD patients have higher CRP levels when compared with PD patients provides support for such hypothesis [29].

Thus, previous evidence consistently supports the hypothesis that a true difference in non-dialysis technique-related

infections exists. Both environmental factors and pathophysiological changes may contribute to this difference. We speculate that the association between dialysis modality and the immune system has the largest impact.

In this study, we described the incidence trend of infectious complications over time. A similar trend has been shown by Dalrymple et al. [4] in their United States Renal Data Systemderived cohort of patients aged 65-100 years. The relatively higher risk for infections related to the vascular access in the early months on HD was consistent with previous results derived from North American cohorts [2, 3]. Previously, the dialysis outcomes and practice patterns study [31] showed that still a large proportion of patients start dialysis with a central venous catheter. Using NECOSAD data, Ocak et al. [24] found that use of central venous catheter at 3 months after the start of dialysis increased the risk for infection-related mortality when compared with arteriovenous access use among elderly patients. We demonstrated that a central venous catheter and an arteriovenous graft are associated with an increased risk for dialysis technique-related infections among HD patients. Therefore, the elevated early risk in HD patients could possibly be diminished by timely preparation of a permanent vascular access, like an arteriovenous fistula. Although a reasonable explanation, we can only speculate whether insufficient access preparation in HD patients might be the explanation for our findings directly after the start of dialysis. Unfortunately, data on the type of vascular access at the baseline of the study and updated information about vascular access were not available in our patients.

In conclusion, our study demonstrated that PD patients are at higher risk for infectious complications compared with HD patients. This difference can be explained by peritonitis and access infections, occurring as a complication of PD. Furthermore, our study confirmed and extended previous findings that suggested an increased risk for non-dialysis techniquerelated infections in HD patients, like pneumonia. The pathophysiological link between dialysis modality and the immune system may explain the difference in non-dialysis techniquerelated infection risk between HD and PD patients. However, further studies are needed to test the assumptions and identify the most important ones. We feel that early and intensive counselling is needed for every patient to make a timely modality decision resulting in on-time preparation for the modality of choice and potential prevention of infectious events. Furthermore, during the counselling for dialysis, substantial attention should be paid to preventative measures for infectious events.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxford-journals.org.

ACKNOWLEDGEMENTS

We thank the trial nurses, participating dialysis centres and data managers of the NECOSAD study for collection and management of the data. We gratefully thank all patients who participated in the NECOSAD study. This work was supported by an ERA-EDTA short-term fellowship grant (STF-124). The ERA-EDTA was not involved in the collection, interpretation and analysis of the data, or in the decision for writing and submitting this report for publication.

CONFLICT OF INTEREST STATEMENT

The authors have none to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

(See related article by Collier and Davenport. Reducing the risk of infection in end-stage kidney failure patients treated by dialysis. *Nephrol Dial Transplant* 2014; 29: 2158–2161.)

REFERENCES

ORIGINAL ARTICLE

- Allon M, Radeva M, Bailey J et al. The spectrum of infection-related morbidity in hospitalized haemodialysis patients. Nephrol Dial Transplant 2005; 20: 1180–1186
- Aslam N, Bernardini J, Fried L *et al.* Comparison of infectious complications between incident hemodialysis and peritoneal dialysis patients. Clin J Am Soc Nephrol 2006; 1: 1226–1233
- Chavers BM, Solid CA, Gilbertson DT *et al.* Infection-related hospitalization rates in pediatric versus adult patients with end-stage renal disease in the United States. J Am Soc Nephrol 2007; 18: 952–959
- Dalrymple LS, Johansen KL, Chertow GM *et al.* Infection-related hospitalizations in older patients with ESRD. Am J Kidney Dis 2010; 56: 522–530
- Williams VR, Quinn R, Callery S *et al*. The impact of treatment modality on infection-related hospitalization rates in peritoneal dialysis and hemodialysis patients. Perit Dial Int 2011; 31: 440–449
- Collins AJ, Foley RN, Chavers B *et al.* United States Renal Data System 2011 Annual Data Report: atlas of chronic kidney disease and end-stage renal disease in the United States. Am J Kidney Dis 2012; 59: A7, e1–A7, 420
- Lafrance JP, Rahme E, Iqbal S *et al*. Association of dialysis modality with risk for infection-related hospitalization: a propensity score-matched cohort analysis. Clin J Am Soc Nephrol 2012; 7: 1598–1605
- de Jager DJ, Grootendorst DC, Jager KJ *et al.* Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA 2009; 302: 1782–1789
- Kato S, Chmielewski M, Honda H et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol 2008; 3: 1526–1533
- Ando M, Shibuya A, Yasuda M *et al*. Impairment of innate cellular response to in vitro stimuli in patients on continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2005; 20: 2497–2503
- Anding K, Gross P, Rost JM *et al.* The influence of uraemia and haemodialysis on neutrophil phagocytosis and antimicrobial killing. Nephrol Dial Transplant 2003; 18: 2067–2073
- Guo H, Liu J, Collins AJ et al. Pneumonia in incident dialysis patients the United States renal data system. Nephrol Dial Transplant 2008; 23: 680–686

- Krediet RT, Boeschoten EW, Dekker FW. Are the high mortality rates in dialysis patients mainly due to cardiovascular causes? Nephrol Dial Transplant 2012; 27: 481–483
- Slinin Y, Foley RN, Collins AJ. Clinical epidemiology of pneumonia in hemodialysis patients: the USRDS waves 1, 3, and 4 study. Kidney Int 2006; 70: 1135–1141
- 15. van Dijk PC, Jager KJ, de Charro F *et al*.Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. Nephrol Dial Transplant 2001; 16: 1120–1129
- Khan IH, Catto GR, Edward N et al. Influence of coexisting disease on survival on renal-replacement therapy. Lancet 1993; 13: 415–418
- Van Manen JG, Korevaar JC, Dekker FW *et al.* How to adjust for comorbidity in survival studies in ESRD patients: a comparison of different indices. Am J Kidney Dis 2002; 40: 82–89
- Van Manen JG, Korevaar JC, Dekker FW *et al.* Adjustment for comorbidity in studies on health status in ESRD patients: which comorbidity index to use? J Am Soc Nephrol 2003; 14: 478–485
- Sussman M. Molecular Medical Microbiology. 1st edn. USA: Academic Press, 2002
- Strelkauskas A, Strelkauskas J, Moszyk-Strelkauskas D. Requirements for Infection. Microbiology: A Clinical Approach. 1st edn. USA: Garland Science, 2009
- Vanderschueren S, Del Biondo E, Ruttens D et al. Inflammation of unknown origin versus fever of unknown origin: two of a kind. Eur J Intern Med 2009; 20: 415–418
- 22. Li PK, Szeto CC, Piraino B *et al.* Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int 2010; 30: 393–423
- Hernán MA, Robins JM. Estimating causal effects from epidemiological data. J Epidemiol Community Health 2006; 60: 578–586
- Ocak G, Halbesma N, le Cessie S *et al.* Haemodialysis catheters increase mortality as compared to arteriovenous accesses especially in elderly patients. Nephrol Dial Transplant 2011; 26: 2611–2617
- Ipp H, Zemlin A. The paradox of the immune response in HIV infection: when inflammation becomes harmful. Clin Chim Acta 2013; 416: 96–99
- Fusshoeller A, Plail M, Grabensee B *et al.* Biocompatibility pattern of a bicarbonate/lactate-buffered peritoneal dialysis fluid in APD: a prospective, randomized study. Nephrol Dial Transplant 2004; 19: 2101–2106
- Chung SH, Heimburger O, Stenvinkel P *et al.* Association between residual renal function, inflammation and patient survival in new peritoneal dialysis patients. Nephrol Dial Transplant 2003; 18: 590–597
- Pecoits-Filho R, Heimburger O, Barany P *et al.* Associations between circulating inflammatory markers and residual renal function in CRF patients. Am J Kidney Dis 2003; 41: 1212–1218
- Haubitz M, Brunkhorst R, Wrenger E *et al.* Chronic induction of C-reactive protein by hemodialysis, but not by peritoneal dialysis therapy. Perit Dial Int 1996; 16: 158–162
- Lavin-Gomez BA, Palomar-Fontanet R, Gago-Fraile M et al. Inflammation markers, chronic kidney disease, and renal replacement therapy. Adv Perit Dial 2011; 27: 33–37
- Ethier J, Mendelssohn DC, Elder SJ et al. Vascular access use and outcomes: an international perspective from the Dialysis Outcomes and Practice Patterns Study. Nephrol Dial Transplant 2008; 23: 3219–3226

Received for publication: 27.3.2014; Accepted in revised form: 30.7.2014