RISK AND PROGNOSIS OF BACTEREMIA AND FUNGEMIA AMONG PERITONEAL DIALYSIS PATIENTS: A POPULATION-BASED COHORT STUDY

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◆ **Background:** The incidence of bacteremia and fungemia (BAF) is largely unknown in end-stage renal disease (ESRD) patients initiating peritoneal dialysis (PD).

◆ **Objective:** The main objective was to estimate and compare incidence rates of first episodes of BAF in incident PD patients and a comparison cohort. A secondary objective was to compare causative agents and 30-day post-BAF mortality between PD patients and the comparison cohort.

◆ **Methods:** Design: Observational cohort study. Setting: Central and North Denmark regions. Participants: patients who initiated PD during 1995 – 2010. For each patient we sampled up to 10 controls from the general population matched on age, sex, and municipality.

◆ **Main outcome:** Data on positive blood cultures were retrieved from electronic microbiology databases covering the 2 regions. We calculated incidence rates (IRs) of first-time BAF for PD patients and population controls. Incidence-rate ratios (IRRs) were calculated to compare these rates. Thirty-day mortality was estimated by Kaplan-Meier analysis.

◆ **Results:** Among 1,024 PD patients and 10,215 population controls, we identified 75 and 282 episodes of BAF, respectively. Incidence rates of BAF were 4.7 (95% confidence interval [CI], 3.8 – 5.9) per 100 person-years of follow-up (PYFU) in PD patients and 0.5 (95% CI, 0.4 – 0.5) per 100 PYFU in population controls (IRR = 10.4; 95% CI, 8.1 – 13.5). In PD patients, the most frequent microorganisms were *Escherichia coli* (18.7%) and *Staphylococcus aureus* (13.3%). *Escherichia coli* (27.3%) also ranked first among population controls. Thirty-day mortality following BAF was 20.8% (95% CI, 12.6 – 31.0) and 20.7% (95% CI, 16.3 – 25.9) among PD patients and population controls, respectively.

◆ **Conclusions:** Peritoneal dialysis patients are at markedly higher risk of BAF than population controls. Causative agents and the 30-day post-BAF mortality were similar in the 2 cohorts.

KEY WORDS: Bacteremia; fungemia; risk; prognosis; peritoneal dialysis.

Infections, including bacteremia and fungemia (BAF), are the second most common cause of death among patients receiving dialysis for end-stage renal disease (ESRD) (1,2). Factors such as malnutrition, placement of catheters in the bloodstream or peritoneal cavity, and persistent uremia may enhance the risk of infection in dialysis patients (3,4).

Whereas BAFs are recognized as major barriers to treatment success in hemodialysis (HD) patients (5), few studies have investigated the risk of BAF and the related term septicemia in ESRD patients on peritoneal dialysis (PD). These studies have reported rates of BAF and/or septicemia varying between 0 and 9.2 per 100 person-years (6–8). Moreover, detailed microbiological information on causative microorganisms and risk factors for BAF in PD patients is lacking. An improved understanding of the incidence, risk factors, causative microorganisms, and outcome of BAF in PD patients could enhance infection control, promote early detection, and ensure appropriate empirical antibiotic treatment.

Therefore, the main objectives of this population-based cohort study were to calculate and compare incidence rates of first-time BAF among incident PD patients and a matched comparison cohort from the general population. Secondary objectives were to describe causative agents, to study potential risk factors for BAF in PD patients, and to analyze post-BAF mortality.

METHODS

STUDY DESIGN AND SETTING

This population-based cohort study was conducted in the North Denmark Region and the Central Denmark Region from 1 January 1995 to 31 December 2010. As of 2010, the population in the study area was 1.83 million people, corresponding to approximately one-third of the total Danish population (9). Within the study area, 4 departments of nephrology offered

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treatment for ESRD during the study period. Since 1990, these departments have reported data to the nationwide Danish Nephrology Registry, which contains information on cause of ESRD, history of renal replacement therapy, and treatment complications. The Registry does not include patients with acute kidney injury. Temporary switches (less than 2–4 weeks) from PD to HD are not registered in the Registry.

Each Danish citizen is assigned a unique 10-digit civil registration number and registered in the Civil Registration System. This system contains information on dates of birth and death, sex, address, municipality, and emigration. Use of the civil registration number for all health care contacts enables accurate linkage between administrative and clinical databases. The Danish National Registry of Patients contains information on all non-psychiatric hospital admissions in Denmark since 1977 and all outpatient contacts since 1995. Variables include discharge diagnoses and dates of admission and discharge. Diagnoses are assigned by the treating physician and coded according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter.

STUDY POPULATION

Using the Danish Nephrology Registry and the Civil Registration System, we identified incident ESRD patients initiating their first PD therapy between 1 January 1995 and 31 December 2010. We included patients who were 16 years or older at the first renal replacement therapy. For comparative analysis, we used the Civil Registration System to sample a cohort of persons from the general population without ESRD (population controls). For each PD patient we sampled up to 10 population controls who were alive at the date of the first PD (matched on age, sex, and municipality). The index date was defined as the date of the first PD therapy for the PD patient and the same date for his/her corresponding population controls. In order to avoid inclusion of patients with ongoing BAF, individuals with positive blood cultures less than 14 days before the index date were excluded.

DEFINITION OF FIRST EPISODE OF BAF

We included only the first episode of BAF in the study period for each patient. All microorganisms isolated in blood cultures obtained within 1 day of the first positive blood culture were considered part of the first episode of BAF except those defined as contaminants (10). In accordance with Weinstein *et al.*, a single positive blood culture for skin bacteria (i.e. coagulase-negative staphylococci, *Micrococcus* species, *Bacillus* species, *Corynebacterium* species, and *Propionibacterium* species) was deemed to represent contamination, unless i) isolated in 2 or more blood cultures drawn separately within a period of 5 days; or ii) isolated within 1 day of a blood culture positive for another microorganism. These criteria correspond to an algorithm developed and validated by Gradel *et al.* (10).

DATA ON BAF

Since September 1994, all blood cultures obtained in the North Denmark Region have been prospectively registered in the electronic laboratory information system ADBakt (Autonik AB, Ramsta, Skoldinge, Sweden). Similarly, the electronic laboratory information system MADS (KMA, AUH, Skejby, Denmark) contains information on all blood cultures analyzed in the Central Denmark Region from 1994 onwards with exception of 2 counties: Ringkjøbing and Viborg. As of 1999, these counties provided data to MADS. Consequently, Ringkjøbing and Viborg counties were included in the study as of 1 January 2000. Both databases contain dates of blood draw and microorganisms isolated, including their antibiotic susceptibility. In both databases, each blood culture set has a unique identification number and the patient's civil registration number.

SOURCE OF BAF

We reviewed the medical records of PD patients with BAF to identify the primary focus for BAF, if possible. We also registered whether the patient had clinical signs and symptoms of infection (fever, chills, or hypotension) according to the Centers for Disease Control and Prevention (CDC) surveillance definition of primary bloodstream infections (11).

DATA ON COMORBIDITY

The Charlson comorbidity index (CCI) is a measure of comorbidity validated for use in prognostic registry-based studies in several different patient populations (12). The CCI score assigns a weight (1, 2, 3, or 6) to each of 19 major disease categories. In this study, we constructed a modified CCI score (m-CCI), which did not include renal disease. The m-CCI was based on the entire discharge history obtained from the Danish National Registry of Patients prior to the person's index date. Based on the m-CCI score, 3 levels of comorbidity were defined: low (m-CCI = 0), medium (m-CCI = 1–2) and high (m-CCI > 2).

DATA ON OTHER VARIABLES

We used the Danish National Diabetes Registry to identify persons who had diabetes diagnosed before their index date (13). Furthermore, we included information on whether the patient had received other types of renal replacement therapy (HD or renal transplantation) before PD (yes/no). Based on information in the Danish Nephrology Registry, we categorized the initial type of PD as continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD).

STATISTICAL ANALYSIS

Follow-Up: In the analysis of incidence rates (IRs) and risk factors for BAF, each person was followed from the index date to the first episode of BAF, death, end of study period, end of PD (except for temporary switches to HD), or emigration

from the study area, whichever came first. In the mortality analyses, participants were followed from the date of their first positive blood culture until the earliest of death, emigration from Denmark, or end of the study period.

Incidence Rates and Incidence Rate Ratios: Incidence rates of first episodes of BAF per 100 person-years of follow-up (PYFU) were calculated for PD patients and population controls both overall and stratified by comorbidity level at index date. These IRs were compared by crude and adjusted incidence-rate ratios (IRRs) using Poisson regression. In the adjusted analysis we included age (16–44, 45–64, ≥65 years at index date), sex, and m-CCI level. Diabetes is a potential confounder in the comparison between PD and the general population controls. Therefore, we performed a sensitivity analysis in which we excluded participants with diabetes at the index date to investigate whether differences in diabetes prevalence between PD patients and controls explained the relative difference in IR.

Risk Factors for BAF in PD Patients: As potential risk factors for BAF, we assessed the following baseline variables: age at index date (16–44, 45–64, ≥65 years), sex, diabetes, initial type of PD, other renal replacement therapy prior to PD, and period of first PD (1995–2002, 2003–2010). We constructed causal diagrams to identify minimal sufficient adjustment sets for each variable, using the web-based software “DAGitty” (14). These variables were included in univariate and multivariate Cox regression models.

Causative Microorganisms: Episodes of BAF with more than 1 microorganism were categorized as polymicrobial. Pathogens were categorized as follows: *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus pneumoniae*, other gram-positive bacteria, *Escherichia coli*, other gram-negative bacteria, anaerobes, fungi, and polymicrobial. For each category, we calculated the number of episodes and pathogen-specific IRs per 1,000 PYFU. These IRs were compared by Poisson regression.

Mortality: For persons with a first episode of BAF, we constructed Kaplan-Meier survival curves and used Cox regression to compare crude and adjusted 30-day all-cause mortality rate ratios (MRRs) using population controls as the reference group. In the adjusted analysis, age at the first episode of BAF (16–44, 45–64, and ≥65 years), sex, and m-CCI level were included as covariates. Patients were not censored at modality change in these analyses.

In the Cox regression analyses, the requisite proportional hazards assumption was assessed graphically. None of the variables had missing data. Stata version 11.0 (Statacorp, College Station, TX, USA) was used for the statistical analyses. The study was approved by the Danish Data Protection Agency (#2013-41-1524) and the Danish National Board of Health (#3-3013-7491).

RESULTS

STUDY POPULATION

We identified 1,031 incident PD patients during the study period. Seven PD patients and their 70 corresponding population controls were excluded due to an episode of BAF registered less than 14 days prior to the index date. Consequently, the final study population consisted of 1,024 PD patients and 10,215 population controls providing 1,594 and 62,521 PYFU, respectively (Table 1). Median time of follow-up was 1.1 years (interquartile range [IQR], 0.4–2.2) for PD patients and 5.5 (IQR, 2.9–9.0) years for population controls. Reasons for end of follow-up in the analyses of risk and risk factors for BAF were as follows: 41 PD patients (4.0%) and 1,060 (10.4%) population controls emigrated from the study area, 46 (4.5%) patients ended PD treatment due to improved kidney function, 395 (38.6%) PD patients changed dialysis modality to HD, and 186 (18.2%) had a kidney transplantation. No participants emigrated during the first 30 post-BAF days.

INCIDENCE RATES

We identified 75 episodes of BAF in PD patients and 282 episodes of BAF in population controls. Incidence rates of BAF were 4.7 (95% CI, 3.8–5.9) per 100 PYFU in PD patients and 0.5 (95% CI, 0.4–0.5) per 100 PYFU in population controls (crude IRR = 10.4 (95% CI, 8.1–13.5)). In the sensitivity analysis we found that the IRR remained unchanged after excluding participants with diabetes at the index date (IRR = 10.4 [95% CI, 7.6–14.3]). When adjusted for sex, age, and m-CCI level, PD patients had a 5.4-fold (95% CI, 4.1–7.1) higher risk of BAF than the population controls. Peritoneal dialysis patients with a low comorbidity level had a 12-fold higher risk of BAF than the controls with a low level of comorbidity (adjusted IRR = 12.3 (95% CI, 7.3–20.7) (Table 2). In patients and controls with medium and high levels of comorbidity the adjusted IRRs were 4.7 (95% CI, 2.9–7.5) and 4.1 (95% CI, 2.7–6.3), respectively.

RISK FACTORS FOR BAF

Table 3 depicts the results of the risk factor analyses and contains links to the causal diagrams. In the adjusted analyses, APD patients had a 1.6-fold (95% CI, 0.9–2.6) increased risk of BAF compared to patients who had CAPD as first PD (Table 3). High age was not associated with increased risk of BAF.

CAUSATIVE MICROORGANISMS

The overall pattern of microorganisms was similar among PD patients and population controls (Table 4). *Escherichia coli* (18.7%) and *S. aureus* (13.3%) were the most common microorganisms in PD patients (Table 4). Monomicrobial fungemia accounted for only 1 and 5 episodes of BAF in PD patients and

TABLE 1
Baseline Characteristics of the Study Population

	Peritoneal dialysis		Population controls ^c	
	N	%	N	%
Number of persons	1,024	100.0	10,215	100.0
Residence at index date ^a				
Central Denmark region	744	72.7	7,440	72.8
North Denmark region	280	27.3	2,775	27.2
Period of study entry				
1995–2002	420	41.0	4,191	41.0
2003–2010	604	59.0	6,024	59.0
Age at index date				
16–44 years	171	16.7	1,708	16.7
45–64 years	405	39.6	4,093	40.1
≥65 years	448	43.8	4,414	43.2
Male sex	621	60.6	6,185	60.6
Comorbidity level (m-CCI) ^b at index date				
Low	320	31.3	7,138	69.9
Medium	308	30.1	2,389	23.4
High	396	38.7	688	6.7
Diabetes at index date	316	30.9	708	6.9
Cause of renal failure				
Glomerulonephritis	133	13.0	—	—
Diabetes mellitus (type I & II)	245	23.9	—	—
Chronic interstitial nephritis	118	11.5	—	—
Hypertension	83	8.1	—	—
Unspecified chronic renal failure	302	29.5	—	—
Polycystic kidney disease	88	8.6	—	—
Other	55	5.4	—	—
Initial type of peritoneal dialysis				
CAPD	559	54.6	—	—
APD	465	45.4	—	—
Other RRT prior to peritoneal dialysis				
Yes	197	19.2	—	—
No	827	80.8	—	—

CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; RR = renal replacement therapy.

^a Index date: Date of first treatment with peritoneal dialysis for peritoneal dialysis patients and their corresponding population controls.

^b Three levels of comorbidity were created based on the modified Charlson comorbidity index score (m-CCI) at the index date “Low” (m-CCI = 0), “Medium” (m-CCI 1–2), and “High” (m-CCI > 2).

^c For each patient on peritoneal dialysis, ≤10 persons from the background population were sampled matched on age, gender, and municipality. See text for details.

population controls, respectively. Coagulase-negative staphylococci were isolated in 3 episodes of monomicrobial BAF and 2 episodes of polymicrobial BAF in PD patients. No episodes were caused by methicillin-resistant *S. aureus*. In PD patients, 7 episodes (9.3%) were caused by *Klebsiella pneumoniae*. Figure 1 displays crude IRRs of BAF by causative microorganism. The increased incidence of BAF was not restricted to typical access site-related pathogens such as coagulase-negative staphylococci and *S. aureus*.

SOURCE OF BAF IN PD PATIENTS

We reviewed the medical records of 73 of the 75 PD patients with BAF (2 medical records were missing in the archives). A

primary focus of infection could be identified in 60 patients. Peritonitis was the primary focus of BAF in 15 episodes (20.6%). In 13 of these episodes the same microorganism was identified in the peritoneal effluent, whereas 2 episodes had negative cultures of peritoneal effluent. Urinary tract (12 episodes, 16%) and respiratory tract (10 episodes, 14%) infections were also common foci in BAF. In 5 episodes (7%) the focus was bone and/or joint infection. One episode complicated an exit-site infection, and 5 episodes had a central venous catheter as the suspected focus. Among the 5 patients with central venous catheters, 2 were planning to change modality to HD and 1 patient recently changed modality from HD to PD. The remaining 2 patients were on PD but had a ventral venous catheter because of concurrent medical conditions.

TABLE 2
Incidence Rates^a 1995–2010 by Level of Comorbidity

Level of comorbidity ^b	N	IR ^c (95% CI)	Crude IRR (95% CI)	Adjusted IRR ^c (95% CI)
Low				
Population comparisons	121	0.3 (0.2–0.3)	1 (Reference)	1 (Reference)
Peritoneal dialysis patients	16	3.2 (2.0–5.2)	12.5 (7.4–21.0)	12.3 (7.3–20.1)
Medium				
Population comparisons	108	0.8 (0.7–1.0)	1 (Reference)	1 (Reference)
Peritoneal dialysis patients	20	4.0 (2.6–6.2)	4.7 (2.9–7.6)	4.7 (2.9–7.5)
High				
Population comparisons	53	1.9 (1.5–2.5)	1 (Reference)	1 (Reference)
Peritoneal dialysis patients	39	6.5 (4.8–8.9)	3.4 (2.2–5.1)	4.1 (2.7–6.3)

IR = incidence rate; IRR = incidence-rate ratio; CI = confidence interval; BAF = bacteremia and fungemia; PD = peritoneal dialysis.

^a Per 100 person years of follow-up of first episodes of BAF among PD patients and population controls.

^b Three levels of comorbidity were created based on the modified Charlson comorbidity index score (m-CCI) at the index date “Low” (m-CCI = 0), “Medium” (m-CCI 1–2), and “High” (m-CCI > 2).

^c Adjusted for age and sex using Poisson regression. See text for details.

TABLE 3
Potential Risk Factors of BAF Among PD Patients

Variable	Hazard ratio ^a (95% CI)	Adjusted hazard ratio ^{a,b} (95% CI)	Variables in adjusted model ^b (link to causal diagram)
Sex			Sex (15)
Men	1 (Ref.)	1 (Ref.)	
Women	0.6 (0.4–1.1)	0.6 (0.4–1.1)	
Age at index date (years)			Age, period, sex (16)
16–44	1 (Ref.)	1 (Ref.)	
45–64	1.1 (0.5–2.4)	1.1 (0.5–2.3)	
≥65	1.1 (0.5–2.2)	1.0 (0.5–2.1)	
Diabetes at index date			Diabetes at index date, age, sex (17)
No	1 (Ref.)	1 (Ref.)	
Yes	1.3 (0.8–2.1)	1.3 (0.8–2.1)	
Type of first PD			Type of PD, age, period, level of comorbidity ^c (18)
CAPD	1 (Ref.)	1 (Ref.)	
APD	1.5 (0.9–2.4)	1.6 (0.9–2.6)	
RRT before PD			RRT before PD, age, period, level of comorbidity ^c (19)
No	1 (Ref.)	1 (Ref.)	
Yes	1.5 (0.9–2.5)	1.4 (0.8–2.5)	
Period of first PD			Period (20)
1995–2002	1 (Ref.)	1 (Ref.)	
2003–2010	0.8 (0.5–1.2)	0.8 (0.5–1.2)	

BAF = bacteremia and fungemia; PD = peritoneal dialysis; CI = confidence interval; Ref. = reference; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; RRT = renal replacement therapy.

^a Calculated using Cox regression.

^b Minimal adjustment sets for estimating the total effect of each exposure were defined according to causal diagrams.

^c Three levels of comorbidity were created based on the modified Charlson comorbidity index score (m-CCI) at the date of first transplantation “Low” (m-CCI = 0), “Medium” (m-CCI 1–2), and “High” (m-CCI > 2). See text for details.

Among the 73 patients, 72 (99%) had clinical signs of infection according to the CDC definition. The last patient had peritonitis and the same microorganism was isolated in the peritoneal effluent.

MORTALITY

The 30-day mortality was 20.0% (95% CI, 12.6 – 31.0) in PD patients and 20.7% (95% CI, 16.3 – 25.9) in population

TABLE 4
Causative Microorganisms in 75 and 282 Episodes of BAF in PD Patients and Matched Population Controls

	PD				Population controls			
	<i>N</i>	(%)	Incidence rate ^a (95% CI)		<i>N</i>	(%) ^a	Incidence rate ^a (95% CI)	
Aerobic and facultative anaerobic bacteria								
Gram-positive								
<i>Staphylococcus aureus</i>	10	13.3	6.3	(3.4–11.7)	30	10.6	0.5	(0.3–0.7)
Coagulase-negative staphylococci	3	4.0	1.9	(0.6–5.8)	12	4.3	0.2	(0.1–0.3)
<i>Streptococcus pneumoniae</i>	4	5.3	2.5	(0.9–6.7)	28	9.9	0.4	(0.3–0.6)
Other gram-positive	13	17.3	8.2	(4.7–14.0)	32	11.4	0.5	(0.4–0.7)
Gram-negative								
<i>Escherichia coli</i>	14	18.7	8.8	(5.2–14.8)	77	27.3	1.2	(1.0–1.5)
Miscellaneous gram-negative	17	22.7	10.7	(6.6–17.2)	52	18.4	0.8	(0.6–1.1)
Anaerobic, fungi and polymicrobial								
Anaerobic	4	5.3	2.5	(0.9–6.7)	9	3.2	0.1	(0.1–0.3)
Polymicrobial and fungi ^b	10	13.3	6.3	(3.4–11.7)	42	14.9	0.7	(0.5–0.9)

BAF = bacteremia and fungemia; PD = peritoneal dialysis; CI = confidence interval.

^a Per 1,000 person years.

^b Monomicrobial fungemia accounted for one episode of BAF in PD patients and 5 episodes of BAF in population controls.

Figure 1 — Incidence-rate ratios of BAF by category of microorganism among PD patients and controls from the general population. IRR = incidence-rate ratio; CI = confidence interval; BAF = bacteremia and fungemia; PD = peritoneal dialysis.

controls, respectively (Figure 2). The crude and adjusted 30-day MRRs with population controls as reference group were 1.0 (95% CI, 0.5 – 1.7) and 1.1 (95% CI, 0.6 – 2.0), respectively.

DISCUSSION

In this study, we found that BAF is a common condition in PD patients. Compared with persons from the general population, PD patients had a more than 5-fold increased risk of BAF when adjusting for age, sex, and level of comorbidity. The excess risk of BAF was mainly attributable to pathogens associated with peritonitis, respiratory, and urinary tract infections. Finally, despite PD patients' frequent and easy access to tertiary

Figure 2 — Cumulative mortality following first episode of BAF in PD patients and controls from the general population. BAF = bacteremia and fungemia; PD = peritoneal dialysis.

medical care units, short-term mortality following an episode of BAF was high.

Our study has several strengths. First and foremost, we used population-based cohorts with a high degree of data completeness. Loss to follow-up was limited to those who emigrated from the study area. Moreover, the use of the electronic microbiology databases allowed us to provide detailed information on microorganisms.

The study also has some limitations. We created 3 levels of comorbidity based on the hospital discharge history of each participant. Although the relative risks in the groups with little or high levels of comorbidity differed little, this approach may not adjust fully for differences in comorbidity (i.e. residual confounding). Physicians may have had a lower threshold for hospital admission and for ordering of blood-cultures in PD

patients with signs and/or symptoms of infections than in population controls. Consequently, BAF may be less underdiagnosed in PD patients than in the population controls, which could have caused us to overestimate the relative risk. Importantly, the results of our medical record review and the validation study by Gradel *et al.* suggest that the positive predictive value of a BAF episode according to our definition was very high (10). Although we may have misclassified some isolates of skin bacteria as contamination, the interpretation of a single-positive blood culture with skin bacteria is often challenging, even with access to comprehensive clinical data, and we consider this to be a minor source of bias. We were unable to adjust for use of immune suppressive therapy in the assessment of diabetes as a potential risk factor for BAF. Of note, PD patients have a higher general risk of death than persons from the general population, which may bias BAF-associated relative mortality during long-term follow-up after BAF. However, as we studied 30-day mortality, the impact of this potential bias is limited.

Few studies have investigated the risk of BAF in PD patients. Contrasting our findings, no episodes of BAF were observed among 62 incident PD patients with a median follow-up of 15 months in a US single-center study (6). However, the number of participants was very low and few missed cases may explain the discrepancy. Wang *et al.* reported 3.6 episodes of bacteremia per 100 PYFU among 532 PD patients in a Taiwanese single-center study, which is slightly lower than our estimate (8). A possible explanation is that Wang *et al.* included prevalent PD patients, which introduces a risk of selection bias. In a large US registry-based study on incident PD patients, Foley *et al.* reported annual IRs of first admissions for septicemia during 1991 – 1999. These IRs varied between 5.7 per 100 PYFU and 9.2 per 100 PYFU (7). Importantly, septicemia was defined by hospital discharge diagnoses, which also include culture-negative sepsis (21,22). Therefore, the results of these studies cannot be directly compared to our results. Interestingly, the IR of BAF in PD patients was markedly lower than the 13.7 per 100 PYFU among ESRD patients managed on HD recently reported in another study from our group (23).

Surprisingly, high age was not associated with increased risk among PD patients in the present study. This contrasts the findings by Powe *et al.* who found that age above 65 years was a risk factor for septicemia in 913 incident PD patients in the US (24). However, their study did not take changes in modality of renal replacement therapy during follow-up into account. Several factors may explain our findings: First, clinical signs of BAF may be more discrete in older PD patients and BAF may therefore be under-diagnosed. Second, in the study area, old and fragile patients often received home assistance for PD, which likely reduced infection risk and facilitated early admission in case of signs of infection. Unexpectedly, we observed that short-term mortality following BAF in PD patients was similar to that of population controls with BAF. However, it is plausible that clinicians are more observant of early signs of infection in PD patients. Furthermore, PD patients are also likely to react earlier than population controls on signs and

symptoms of infection. These factors may act to reduce mortality from BAF in PD patients.

There are few published data on causative microorganisms in PD patients with BAF. In the study by Wang *et al.* with 69 episodes of bacteremia, coagulase-negative staphylococci and *S. aureus* accounted for 21% and 16% of 94 microorganisms, respectively. However, the distribution of microorganisms in monomicrobial episodes was not specified (8). Similarly, Abbott *et al.* reported that 38% of the episodes of septicemia were caused by staphylococci in a large US study (25). Importantly, Abbott *et al.* used discharge diagnoses whereas our definition was based on positive blood cultures. These differences complicate comparisons of the studies. In our study, we had access to complete blood culture data in a well-defined population. Combined with the conservative algorithm for coagulase-negative staphylococci, this may contribute to the lower proportion of coagulase-negative staphylococci in the present study. In our study area, screening for nasal carriage of *S. aureus* and nasal decolonization of carriers with mupirocin is widely used in PD patients, which may lower the rate of *S. aureus* bacteremia in these patients. Nonetheless, the risk of *S. aureus* bacteremia remained markedly higher in PD patients than in population controls. Reporting rates of BAF for specific microorganisms may facilitate comparisons across future studies and facilitate monitoring of infection control programs (26).

Peritonitis, exit-site infections, and tunnel infections are classical infectious complications of PD. Within the study area, peritonitis occurred at a rate of 1 per 26 patient-months in 2000 – 2004 (11). Our results are therefore in accord with previous studies indicating that BAF is uncommon in PD patients with peritonitis (27). Nonetheless, optimized infection control including careful training (patients and clinicians) and quality control programs can reduce peritonitis rates markedly and are thus likely to reduce BAF risk (28). Furthermore, pneumococcal vaccination in PD patients may also be cost-effective.

CONCLUSIONS

In conclusion, the risk of BAF in PD patients is high and a first episode of BAF is associated with considerable short-term mortality. Thus, BAF is a clinically important infection to consider in studies on prevention of infections in PD patients. Peritonitis and the urinary tract were the most common sources of BAF in PD patients. Yet, the pattern of microorganism resembled that of the comparison cohort.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

REFERENCES

- de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, *et al.* Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* 2009; 302(16):1782–9.
- National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, US Renal Data System (USRDS). *USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: USRDS; 2013.
- Vaziri ND, Pahl MV, Crum A, Norris K. Effect of uremia on structure and function of immune system. *J Ren Nutr* 2012; 22(1):149–56.
- Ishani A, Collins AJ, Herzog CA, Foley RN. Septicemia, access and cardiovascular disease in dialysis patients: the USRDS Wave 2 study. *Kidney Int* 2005; 68(1):311–8.
- Foley RN. Infections in patients with chronic kidney disease. *Infect Dis Clin North Am* 2007; 21(3):659–72.
- Aslam N, Bernardini J, Fried L, Burr R, Piraino B. Comparison of infectious complications between incident hemodialysis and peritoneal dialysis patients. *Clin J Am Soc Nephrol* 2006; 1(6):1226–33.
- Foley RN, Guo H, Snyder JJ, Gilbertson DT, Collins AJ. Septicemia in the United States dialysis population, 1991 to 1999. *J Am Soc Nephrol* 2004; 15(4):1038–45.
- Wang IK, Chang YC, Liang CC, Chuang FR, Chang CT, Lin HH, *et al.* Bacteremia in hemodialysis and peritoneal dialysis patients. *Internal Med* 2012; 51(9):1015–21.
- Snell JJ. Statistics Denmark [Available at <http://www.statbank.dk/statbank5a/default.asp?w=1920>: updated 3 december 2013; cited 2013 2 December 2013].
- Gradel KO, Knudsen JD, Arpi M, Ostergaard C, Schonheyder HC, Sogaard M, *et al.* Classification of positive blood cultures: computer algorithms versus physicians' assessment—development of tools for surveillance of bloodstream infection prognosis using population-based laboratory databases. *BMC Med Res Methodol* 2012; 12:139.
- Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; 16(3):128–40.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5):373–83.
- Carstensen B, Kristensen JK, Marcussen MM, Borch-Johnsen K. The National Diabetes Register. *Scand J Public Health* 2011; 39(7 Suppl):58–61.
- Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology* 2011; 22(5):745.
- Dalgaard L. Causal diagram. Sex. PD. [Online.] Available at: <http://dagitty.net/dags.html?id=JYM6wA2015>. Accessed 2015.
- Dalgaard L. Causal diagram. Age. PD. [Online.] Available at: <http://dagitty.net/dags.html?id=a7D4lC2015>. Accessed 2015.
- Dalgaard L. Causal diagram. Diabetes. PD. [Online.] Available at: <http://dagitty.net/dags.html?id=ARwOBK2015>. Accessed 2015.
- Dalgaard L. Causal diagram. Type of PD. [Online.] Available at: <http://dagitty.net/dags.html?id=ajA6OR#> 2015. Accessed 2015.
- Dalgaard L. Causal diagram. Renal replacement therapy before PD. [Online.] Available at: <http://dagitty.net/dags.html?id=Grp2GI> 2015. Accessed 2015.
- Dalgaard L. Causal diagram. Period of first PD. [Online.] Available at: <http://dagitty.net/dags.html?id=oC5NYV2015>. Accessed 2015.
- Ollendorf DA, Fendrick AM, Massey K, Williams GR, Oster G. Is sepsis accurately coded on hospital bills? *Value Health* 2002; 5(2):79–81.
- Madsen KM, Schonheyder HC, Kristensen B, Nielsen GL, Sorensen HT. Can hospital discharge diagnosis be used for surveillance of bacteremia? A data quality study of a Danish hospital discharge registry. *Infect Control Hosp Epidemiol* 1998; 19(3):175–80.
- Dalgaard L, Norgaard M, Jespersen B, Jensen-Fangel S, Ostergaard LJ, Schonheyder HC, *et al.* Risk and prognosis of bloodstream infections among patients on chronic hemodialysis: a population-based cohort study. *PLOS ONE* 2015; 10(4):e0124547.
- Powe NR, Jaar B, Furth SL, Hermann J, Briggs W. Septicemia in dialysis patients: incidence, risk factors, and prognosis. *Kidney Int* 1999; 55(3):1081–90.
- Abbott KC, Agodoa LY. Etiology of bacterial septicemia in chronic dialysis patients in the United States. *Clin Nephrol* 2001; 56(2):124–31.
- Piraino B. Approaches to preventing peritonitis based on organism-specific rates. *Perit Dial Int* 2011; 31(6):636–8.
- Morduchowicz G, van Dyk DJ, Wittenberg C, Winkler J, Boner G. Bacteremia complicating peritonitis in peritoneal dialysis patients. *Am J Nephrol* 1993; 13(4):278–80.
- Piraino B, Bernardini J, Brown E, Figueiredo A, Johnson DW, Lye WC, *et al.* ISPD position statement on reducing the risks of peritoneal dialysis-related infections. *Perit Dial Int* 2011; 31(6):614–30.