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Outcomes of *Staphylococcus aureus* Bacteremia in Patients with Chronic Kidney Disease versus without Chronic Kidney Disease

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Abstract

Objectives: *S. aureus* bacteremia (SAB) is a leading cause of infection in patients with chronic kidney disease (CKD). Clinical outcomes associated with SAB in patients with CKD and with non-CKD were compared.

Materials and methods: Laboratory and clinical data from patients who were hospitalized with SAB in a tertiary care hospital were reviewed. Linear regression was used to identify independent predictors of 7-day, 30-day, and 90-day mortality.

Results and discussion: A total of 79 patients with CKD and 92 patients without CKD were enrolled from Mar 2014 to Dec 2016. Seven-day and 90-day mortality were increased in patients with CKD compared to patients with non-CKD (7-day mortality, 19% *vs.* 8.7%, p=0.011; 30-day mortality, 30.4% *vs.* 23.9%, p=0.058; 90-day mortality, 38.0% *vs.* 26.1%, p=0.002). Difference of Pitt bacteremia score and persistent bacteremia longer than 7 days among both groups was not statistically significant. High SOFA (sequential organ failure assessment) score and proportion of administration of inappropriate antibiotics was associated with CKD.

Conclusion: SAB bacteremia in CKD was combined with high SOFA score. Administration of inappropriate antibiotics might cause high mortality in patients with CKD.

Keywords: *Staphylococcus aureus*; Bacteremia; Chronic kidney disease

Introduction

Patients with chronic kidney disease (CKD) are at a greater risk for *S. aureus* bacteremia (SAB) [1-5]. The annual incidence of SAB in patients with CKD has been reported to range from 6 to 27% in other countries [3,6]. SAB is frequently complicated with endocarditis, osteomyelitis, meningitis, and metastatic abscesses [7-9]. Patients with CKD who are acquired SAB are at greater risk of death than patients without CKD [10].

Use of intravascular catheters, fluid overload, accumulation of dialysis fluid in the abdomen affecting the lung volume, and the negative impact of the uremic state on immune function, are all potential factors for bacteremia among patients with CKD [11-13]. Although SAB is relatively common among CKD patients, case fatality in patients with SAB as well as risk factors associated with mortality are not well characterized.

The objectives of this study were to investigate and compare the outcomes of SAB among CKD patients to that of non-CKD controls and identify risk factors for high-case fatality in patients with CKD following SAB.

Materials and methods

Patients and settings

We retrospectively reviewed the data of patients with SAB who were hospitalized in a tertiary care hospital from Mar 2014 to Dec 2016. If multiple episodes of SAB occurred in one patient, only the first episode was enrolled. We defined patients with CKD as patients who had serum creatinine level 1.4 for at least 90 days or patients who had renal replacement therapy (i.e. peritoneal dialysis or haemodialysis). Patients who were at least 18 years of age and had no prior recorded SAB episode at the time of SAB diagnosis were included in the study.

Data collection

Demographic data and case-fatality was collected. In this study, we calculated Pitt bacteremia score and SOFA (sequential organ failure assessment) score for each study participant as it mentioned before. Persistent bacteremia was defined as bacteremia prolonged more than 7 days with positive blood culture.

Statistical analyses

Risk factors: Cox regression was used to determine hazard ratios and identify risk factors for the first episode of SAB in patients with CKD. The following variables were entered into the model: age, gender, comorbidity, Pitt bacteremia score, SOFA score.

Source of SAB and methicillin resistance: The source of incident SAB cases was tabulated (primary bacteremia, catheter-related blood

stream infection, infective endocarditis, pneumonia, osteomyelitis, arthritis, skin and soft tissue infection, surgical site infection, etc.) as well as the susceptibility of the isolated strains to methicillin (resistant, sensitive, or unknown).

Case fatality rates following SAB: We computed Kaplan-Meier estimates for the 7, 30 and 90th day case fatality rate of patients according to CKD and their matched population controls. The resulting survival curves were examined for differences by log-rank test. We used SPSS statistics software, version 25.0 (IBM) for statistical analyses. The study was approved by the Chungnam National University Hospital Institutional Review Board.

Results

A total of 265 patients were reported to have *S. aureus* from blood culture during the study period. Ninety four patients were excluded from the analysis because they didn't show SIRS or other pathogens were confirmed. Seventy-nine patients with CKD and 92 patients without CKD were enrolled for the analysis. The demographic characteristics were shown in Table 1. Patents with CKD showed male predominance and 36 (45.6%) had renal replacement therapy through hemodialysis (*via* tunneled HD catheter, 17; *via* arteriovenous fistula or graft, 19). CRBSI was most common source of SAB in both groups, despite primary bacteremia was more frequent in patients with CKD.

Variables	CKD patients (N=79)	Non-CKD patients (N=92)	p-value
Age, range (median), years	34-90 (67)	19-101 (68.5)	--
Male	55 (69.6%)	50 (54.3%)	0.041
Underlying conditions			
Diabetes	31 (49.3%)	21 (22.9%)	<0.0001
Malignancy	10 (12.7%)	28 (30.4%)	0.005
Renal replacement therapy			
HD *via* perm-catheter	17 (21.5%)	NA	--
HD *via* AVF or AVG	19 (24.1%)	NA	--
MRSA (%)	44 (58.7%)	44 (55.7%)	--
Source of SAB			
Primary bacteremia	21 (26.6%)	18 (19.6%)	--
CRBSI	24 (30.4%)	30 (32.6%)	--
Non-tunneled catheter	4 (16%)	15 (50%)	--
PICC	5 (20.8%)	3 (10%)	--
Hickmann-Broivac catheter	1 (4%)	3 (10%)	--
Chemoport	5 (20.8%)	9 (30%)	--
Tunneled HD catheter	8 (32%)	18 (19.6%)	--
Spondylitis	9 (11.4%)	2 (2.2%)	--
Pneumonia	5 (6.3%)	2 (2.2%)	0.067
UTI	2 (2.6%)	NA	<0.0001
AVF or AVG site infection	9 (11.4%)	3 (3.3%)	--
Endocarditis	1 (1.3%)	8 (8.7%)	--
Arthritis	3 (3.8%)	1.22 ± 2.09	--
Pitt bacteremia score, mean ± SD	1.88 ± 2.697	1.86 ± 2.829	--
SOFA score, mean ± SD	5.49 ± 5.25	--	--

Table 1: Demographic characteristics of patients.

Pitt bacteremia score was zero in 34 patients (43%) of CKD patients and 47 patients (51%) of non-CKD patients. Mean Pitt bacteremia score was 1.88 ± 2.697 in CKD patients and 1.22 ± 2.09 in non-CKD patients (p=0.067). Mean SOFA score was 5.49 ± 5.25 in CKD patients

and 1.86 ± 2.829 (p <0.0001). The proportion of MRSA and susceptibility patterns was similar in two groups.

The clinical outcomes of SAB were described in Table 2. Seven-day and 90-day mortality was higher in CKD patients with SAB than in non-CKD patients (19% *vs.* 8.7%, p=0.011; 38% *vs.* 26.1%, p=0.002). Persistent bacteremia (bacteremia ≥ 7 days) was more frequent in non-CKD patients than in CKD patients without statistical significance (18.5% *vs.* 12.7%, p=0.16). Appropriate antibiotics for MRSA was not administered in 11 (13.9%) of CKD patients and 7 (7.6%) of non-CKD patients (p=0.026).

Variables	CKD patients (N=79)	Non-CKD patients (N=92)	p-value
7-day fatality	15 (19%)	8 (8.7%)	0.011
30-day fatality	24 (30.4%)	22 (23.9%)	0.058
90-day fatality	30 (38%)	24 (26.1%)	0.002
Persistent bacteremia	10 (12.7%)	17 (18.5%)	0.076
Anti-MRSA therapy inappropriate	11 (13.9%)	7 (7.6%)	0.026

Table 2: Clinical Outcomes of SAB in CKD patients and in non-CKD patients.

Discussion

Catheter access is a well-known risk factor for SAB acquisition in patients irrespective of CKD [10]. Interestingly, primary bacteremia was relatively common in patients with CKD compared to non-CKD patients, although CRBSI was most common source of SAB in both groups. Our analyses revealed that almost half of patients receiving dialysis *via* AVF, AVG, or tunneled HD catheter developed SAB during a 3-year period.

Although 30-day mortality was not different in both groups, we observed that 7-day and 90-day mortality was high in patients with CKD. Pitt bacteremia score and prolonged bacteremia was not different in patients with or without CKD. However, SOFA score was elevated in patients with CKD that organ failure was severe in this group. Considering that patients with malignancy composed 30% of non-CKD group, SAB might cause more damage in patients with CKD compared to patients with malignancy.

Appropriate antimicrobial agents (especially anti-MRSA agents) were not used for 11 patients with CKD and 7 patients without CKD. But, most of these patients were expired within 24 hours after bacteremia started. This means that SAB caused rapid deterioration in patients who are very vulnerable to infection and the use of appropriate antimicrobial agents might not affect the outcome of these patients. For these patients, especially at a high risk of SAB acquisition and of high case-fatality, prophylactic vaccine or other measures to prevent SAB need to be developed in near future.

Our study has several limitations. First, the study was performed with retrospective reviews of electronic medical chart reviews. Investigation of source of SAB was incomplete for some patients. Blood culture from catheter site was not done for some patients, so the proportion of CRBSI might be underestimated. Second, the analysis was limited to admission due to *S. aureus* infection. Thus, patients who were found to have SAV and treated at outpatient clinics were not enrolled. Third, some patients under terminal care for malignancy or liver cirrhosis was not treated with antimicrobial agents. Furthermore, we only included cases with SAB; hence the true impact of invasive SA disease may have been underestimated.

Conclusion

In conclusion, patients with CKD have a greatly increased mortality of SAB compared to patients without CKD. SOFA score and inappropriate antimicrobial use might be related to high fatality in patients with CKD. As there are currently no prophylactic vaccines for SAB, future researches will be to develop other preventive measures and treatment strategies to reduce morbidity and case fatality in patients with CKD

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