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ORIGINAL ARTICLE

Community-onset bacteremia in kidney transplant recipients: The recipients fare well in terms of mortality and kidney injury

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Background: Bloodstream infection is not uncommon in kidney transplant recipients (KTRs) and is associated with mortality, graft loss, and increased medical expenses. Whether these septic patients are more vulnerable to serious complications, resistant strains, or worse clinical outcomes than other patient groups in the community-onset settings remains undetermined.
Methods: A retrospective study was conducted at a medical center in southern Taiwan. Community-onset bacteremia in the KTRs and a control population at the emergency department were identified. Demographic data, clinical characteristics, bacteremic pathogens, antimicrobial resistance, and clinical outcomes were recorded.
Results: Forty-one bacteremic episodes in the KTRs and 82 episodes in control patients were studied. The KTR group had younger age, fewer malignancies, more urosepsis (61% vs. 22%, $p = 0.004$), and fewer biliary tract infections (0% vs. 13.4%, $p = 0.018$). *Escherichia coli* was the most commonly isolated pathogen in both the groups (51.2% and 41.5%, respectively). No *Klebsiella pneumoniae* bacteremia was noted in the KTRs, compared with 14 (17.1%) episodes in the control group ($p = 0.010$). Antimicrobial resistance profiles of bacteremic pathogens were similar (all $p > 0.6$). The KTRs with community-onset bacteremia did not have a worse outcome (in-hospital mortality rate: 2.4% vs. 10%, $p = 0.172$) nor more incomplete

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resolution of kidney injury after acute kidney injury events (21.1% vs. 25%, $p > 0.99$) than the control group.
Conclusion: KTRs with community-onset bacteremia did not fare worse in terms of clinical outcome and kidney injury.

Introduction

Bloodstream infection is not uncommon in kidney transplant recipients (KTRs) and could be lethal. The incidence ranges from 0.7 to 11 episodes/100 patient-year.[1,2] The mortality rate of septicemia was 63% in the 1960s and remained as high as 24.3% even in the 2000s.[1–3] The graft survival and medical expenses are also significantly impacted by the sepsis episodes.[4]

Medical care for KTRs with sepsis is more difficult because they are prone to kidney injury and drug—drug interaction caused by their immunosuppressive agents such as cyclosporin and tacrolimus. The condition is further complicated by the pathogens with variable resistance to cephalosporins and fluoroquinolones, as well as by a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing strains among these patients.[5–7]

Also, the composition of patients visiting the emergency department (ED) changed due to the advances in chemotherapies, antiretroviral therapies, and care for chronic diseases. However, few reports compared the difference between KTRs and other patient groups with bacteremia. We conducted a retrospective study to assess the clinical characteristics, pathogen distribution, and clinical outcome of community-onset bacteremia among KTRs and general population.

Materials and methods

Study design and population

A retrospective study was conducted at a tertiary hospital with approximately 1200 beds in southern Taiwan. All patients older than 18 years with International Classification of Diseases-9 code V420 or kidney transplantation in the discharge diagnosis and positive blood cultures collected at the ED between 2005 and 2010 were included as the case group. All bacteremia episodes were included except those developing within 14 days after previous episodes with identical pathogens. Those patients with graft failure and regular hemodialysis were excluded as they often discontinued their immunosuppressants and had some type of vascular access. In addition, we excluded all cases of hospital-acquired bacteremic episodes.

For each bacteremic episode in the case group, we identified the earlier and following patient with community-onset bacteremia, according to the arrival time in the ED. Two control patients were included for each study case. Patients with regular renal replacement therapy, hospital-acquired infections, or incomplete medical record were replaced by the next eligible patient.

The medical records of the included bacteremic episodes were reviewed. Demographic data, underlying diseases, recent medical intervention, clinical manifestations, laboratory data within the first 24 hours upon presentation, microbiology studies, antimicrobial treatment, length of hospital stays, and clinical outcome were collected. Besides, serum creatinine level before and after the bacteremia episode was recorded. The sources of infection were determined by the investigators based on medical records and radiological or sonographic images.

Microbiology and antimicrobial susceptibility

Blood cultures were collected by the ED staff in two bottles and loaded into the BACTEC 9240 system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Subcultures onto plates with Trypticase soy agar with 5% sheep blood (Becton, Dickinson and Company), eosin—methylene blue agar (Levine agar; Becton, Dickinson and Company), chocolate agar, and CDC anaerobic blood agar (Becton, Dickinson and Company) were performed when the initial results were positive. Biochemical tests and the VITEK automatic identification system (bioMérieux, Marcy-l'Étoile, France) were used for final identification. *In vitro* antimicrobial susceptibility tests of blood isolates were performed by the disc diffusion method on Müller—Hinton agar. The results were interpreted according to the Clinical Laboratory Standard Institute guidelines.[8]

Definitions

Bacteremia was defined as isolation of bacteria from at least one set of blood culture bottles; however, the following bacteria should be isolated from at least two sets of blood cultures in order to classify the infection as "true bacteremia"[9,10]: coagulase-negative staphylococci, aerobic Gram-positive bacilli, *Micrococcus* species, *Clostridium perfringens*, and *Propionibacterium* species. Polymicrobial bacteremia was defined as the isolation of more than one bacterial species from each bacteremic episode. Effective antimicrobial therapy was defined as administration of antibiotics to which the pathogen was susceptible *in vitro*.

The severity of bloodstream infections on presentation was measured by the Pittsburgh bacteremia score, a validated scoring system based on fever, hypotension, mental status, mechanical ventilation, and the presence of cardiac arrest.[11] With regard to the infection types, hospital-acquired infection was defined according to the World

Health Organization definition.[12] Health care-associated infections included infections occurring in patients who received the specialized nursing care or intravenous therapy at home, attended a hospital, received intravenous chemotherapy in the past 30 days, hospitalized for 2 or more days in the past 90 days, or residents of long-term care facilities.[13]

Acute kidney injury (AKI) was defined as a 50% elevation in serum creatinine level within 7 days or an increase of $\geq$0.3 mg/dL within 48 hours. Incomplete resolution of the kidney injury was defined as no normalization of estimated glomerular filtration rate (GFR) to the baseline level within 3 months after the bacteremia onset that could not be attributed to another distinct kidney injury event.[14] Taking the laboratory limitation into consideration, a difference in serum creatinine level of at least 0.2 mg/dL is required to detect GFR changes.

Statistical analysis

All statistical analyses were performed using R version 3.0.2 [R core team (2013), R Foundation for Statistical Computing, Vienna, Austria]. Continuous variables were presented as means $\pm$ standard deviations or medians (1^{st}—3^{rd} quartile) according to the distribution tested by the Shapiro—Wilk test. Student *t* test or Wilcoxon rank-sum test was applied for between-group comparison for normally or non-normally distributed variables, respectively. Category variables were compared by Pearson's χ^2 test or Fisher's exact test when appropriate.

Results

Of the 564 KTRs (53.5% male) in the study period, we identified 40 KTRs with bacteremia. Eight patients on hemodialysis at the onset of bacteremia and a patient with hospital-acquired infection were excluded. Therefore, the KTR group finally included 31 KTRs (with 41 episodes of community-onset bacteremia). The male-to-female ratio was 1:1.4. One patient had four bacteremic episodes and seven experienced two episodes with the minimal interval of 1 month between bacteremic episodes. Eighty-two patients without regular hemodialysis having bacteremic episodes were included as the control group.

The KTR group was younger (49.5 $\pm$ 9.3 vs. 64.9 $\pm$ 14.8 years, $p < 0.001$), none had hepatic cirrhosis (0% vs. 14.6%, $p = 0.037$), and only one had malignancies (3.2% vs. 37.8%, $p < 0.001$). No significant differences in the presence of diabetes mellitus, hypertension, or old stroke were demonstrated in the KTR and control groups (Table 1).[15]

All KTRs received immunosuppressive agents (Table 2). In the KTR group, 28 (68.3%) of the 41 episodes developed >6 months after the kidney transplantation. The proportion of severe sepsis, indicated by a Pittsburgh bacteremia score of 4 or more, was similar in the two groups (7.3% vs. 15.9%, $p = 0.391$). In the KTR group, only one patient underwent recent chemotherapy compared with 12 patients in the control group ($p = 0.064$). The laboratory parameters associated with sepsis, such as leukocytosis, thrombocytopenia, and elevated serum C-reactive protein, were not different. The KTR group had a higher serum creatinine level at initial presentation (1.8 mg/dL vs. 1.0 mg/dL, $p < 0.001$). Half of the KTR group had a certain degree of AKI along with the bacteremia episodes, compared with 39.5% in the control group ($p = 0.164$).

Table 1 Demographic data and comorbidities of the KTRs and the patients without kidney transplant (control) having community-onset bacteremia

Variables	Number of patients (%)		*p*
	KTR group ($n = 31$)	Control group ($n = 82$)	
Age, y (mean $\pm$ SD)	49.5 $\pm$ 9.3	69.4 $\pm$ 14.8	<0.001
Age > 65 y	1 (3.2)	45 (56.1)	<0.001
Sex: male	13 (41.9)	46 (56.1)	0.441
Comorbidities			
Chronic kidney disease[a]	31 (100)	14 (17.1)	<0.001
Hypertension	20 (64.5)	35 (42.7)	0.238
Diabetes mellitus	11 (35.5)	25 (30.5)	0.717
Autoimmune disease	3 (9.7)	2 (2.4)	0.143
Old stroke	2 (6.5)	15 (18.3)	0.236
Congestive heart failure	1 (3.2)	5 (6.1)	>0.99
Malignancy	1 (3.2)	31 (37.8)	<0.001
Hepatic cirrhosis	0 (0)	12 (14.6)	0.037

[a] Chronic kidney disease: definition according to the KDIGO chronic kidney disease guideline.[15].
KDIGO guideline = The Kidney Disease Improving Global Outcomes guideline; KTR = kidney transplant recipients.

The KTR group was more likely to have urinary tract infections (UTIs; 61% vs. 23.2%, $p = 0.004$), but intra-abdominal infections less frequently (9.8% vs. 25.6%, $p = 0.099$), especially biliary tract infections (BTIs; 0% vs. 11%, $p = 0.018$). In the KTR group, acute graft pyelonephritis with local pain or tenderness was discovered in six [24%; 4 male patients (16%)] of the 25 UTI episodes in the KTR group. Polymicrobial bacteremia was detected in one patient in the KTR group and in 11 patients in the control group ($p = 0.104$).

Gram-negative bacilli are the major causes of bacteremia in both groups, accounting for 80.5%% and 65.9% of the patients in the KTR and control groups, respectively ($p = 0.492$; Table 3). *Escherichia coli* was the most common pathogen in both groups and the proportion of ESBL-producing strain was similar (4.9% vs. 6.1%, $p > 0.99$). The control group had more *Klebsiella pneumoniae* bacteremia (0% vs. 17.1%, $p = 0.010$). With regard to antimicrobial susceptibility for Enterobacteriaceae isolates or uropathogens (Table 4), no differences were demonstrated for cephalosporins, gentamicin, or fluoroquinolones (either ciprofloxacin, levofloxacin, or lomefloxacin; all $p > 0.6$).

Timing of effective antimicrobial therapies and clinical outcomes are shown in Table 5. The proportion of initiation of effective therapy within 24 hours was not different between the two groups (80.5% vs. 69.5%, $p = 0.614$). The in-hospital (2.4% vs. 10%, $p = 0.172$) and 1-year (10% vs. 29.6%, $p = 0.061$) mortality rate were lower in the KTR

Table 2 Clinical characteristics, disease severity, laboratory data, and bacteremia source among the KTRs and the patients without kidney transplant (control) having community-onset bacteremia

Variables	Number of cases (%)		*p*
	KTR group ($n = 41$)	Control group ($n = 82$)	
Health-care-associated infection	13 (31.7)	44 (53.7)	0.152
Clinical events within 4 wk before the bacteremia			
Recipient of immunosuppressants	41 (100)	2 (2.4)	<0.001
Hospitalization	10 (24.4)	24 (29.3)	0.666
Surgery	1 (2.4)	2 (2.4)	>0.99
Chemotherapy	1 (2.4)	12 (14.6)	0.064
From symptom onset to ED visit (d)	1 (0—1)	1 (0—2)	0.339
Severity			
Hypotension	7 (17.1)	29 (35.4)	0.110
Pitt bacteremia score ≥ 4	3 (7.3)	13 (15.9)	0.391
Acute altered consciousness	1 (2.4)	12 (14.6)	0.064
Acute kidney injury[a]	20/40 (50)	24/79 (30.4)	0.164
Laboratory data			
WBC $> 9000/mm^3$	30 (73.2)	54 (65.9)	0.723
Absolute neutrophil count $<500/mm^3$	0 (0)	6 (7.3)	0.176
Platelet $< 10^5/mm^3$	7 (17.1)	18 (25)	0.604
Serum creatinine (mg/dL)	1.8 (1.5—2.7)	1.0 (0.8—1.5)	<0.001
C-reactive protein > 100 mg/L[a]	16 (39.0)	42/81 (51.9)	0.417
Source of bacteremia			
Primary bacteremia	6 (14.6)	22 (26.8)	0.220
Urinary tract infection	25 (61.0)	18 (22.0)	0.004
Intra-abdominal infection	4 (9.8)	21 (25.6)	0.099
Biliary tract infection	0 (0)	11 (13.4)	0.018
Liver abscess	0 (0)	3 (3.6)	0.550
Skin and soft-tissue infection	3 (7.3)	5 (6.1)	>0.99
Respiratory tract infection	2 (4.9)	11 (13.4)	0.227
Endovascular infection	1 (2.4)	0 (0)	0.339
Deep neck infection	0 (0)	2 (2.4)	>0.99

[a] Missing data in some patients.
ED = emergency department; KTR = kidney transplant recipients; WBC = white blood cell.

group, although they were not statistically significant. Among the survivors, the length of hospital stay was shorter in the KTR group (6 days vs. 11 days, $p = 0.020$) and the proportions of incomplete resolution of kidney injury after AKI events were similar between the two groups (21.1% vs. 25%, $p > 0.99$).

A further analysis focusing on the patients aged ≤65 years showed that there were 30 patients with 40 bacteremia episodes in the KTR group and 36 patients in the control group. Patients in the nonelderly KTRs group still had higher prevalence of hypertension (63.3% vs. 19.4%, $p = 0.017$) and fewer malignancies (3.3% vs. 33.3%, $p = 0.012$) than those in the nonelderly control group. The in-hospital mortality rate was not statistically different between the two nonelderly groups (2.5% vs. 5.6%, $p = 0.606$). The length of hospital stay among survivors was shorter in the nonelderly patients in the KTRs group (6 days vs. 11 days, $p = 0.018$).

Discussion

As described in previous studies, UTIs represent the majority of bacteremia source among the KTRs.[16,17] The high proportion of urosepsis, accounting for 61% of bacteremia source compared with 30—48% in previous studies, might be attributed to the community-onset settings, which limited the numbers of vascular catheter-related infection mostly occurring in the hospitals.[1,2,6,17] The age and male-to-female ratio may influence the results, because women are more likely to experience UTIs and young men have a lower risk, as compared with older men.[18] We observed a similar condition in the KTR group with the male-to-female ratio of 1:5.3, which echoed the findings of a previous study showing an odds ratio of 5.8 for females to develop UTIs among the KTRs.[19] By contrast, patients with urosepsis in the control group had a male-to-female ratio of 1:0.64 and a mean age of 64.8 years.

Virtually all urosepsis episodes in the KTR group met the definition of acute graft pyelonephritis, that is, fever with one or more of the following clinical symptoms, signs, or biological abnormalities: painful graft, chills, cystitis, dysuria, pyuria, bacteriuria, and increased serum creatinine level.[20,21] However, only 24% of the patients in the KTR group had local symptoms or signs in the transplanted kidneys. Some authors pointed out that the loss of nerve connection at the transplants might explain this phenomenon of infrequent localized tenderness in the transplants.[22]

Table 3 Causative pathogens of bacteremia in the KTRs and the patients without kidney transplant (control)

Variables	Number of cases (%)		*p*
	KTR group (n = 41)	Control group (n = 82)	
Gram-negative aerobes	33 (80.5)	54 (65.9)	0.492
Escherichia coli	21 (51.2)	34 (41.5)	0.530
ESBL-producing *E. coli*	2 (4.9)	5 (6.10)	>0.99
Klebsiella pneumoniae	0 (0)	14 (17.1)	0.010
Salmonella enteritidis	3 (7.3)	2 (2.4)	0.338
Pseudomonas aeruginosa	2 (4.9)	2 (2.4)	0.604
Proteus mirabilis	2 (4.9)	1 (1.2)	0.268
Enterobacter cloacae	1 (2.4)	2 (2.4)	>0.99
Brevundimonas vesicularis	1 (2.4)	0 (0)	0.339
Moraxella spp.	1 (2.4)	0 (0)	0.339
Aeromonas spp.	0 (0)	2 (2.4)	>0.99
Kluyvera spp.	0 (0)	1 (1.2)	>0.99
Gram-positive aerobes	6 (14.6)	23 (28.0)	0.185
Staphylococcus species	2 (4.9)	11 (13.4)	0.227
Methicillin-resistant *Staphylococcus aureus*	0 (0)	2 (2.4)	>0.99
Streptococcus species	4 (9.8)	12 (14.6)	0.582
Enterococcus species	1 (2.4)	3 (3.6)	>0.99
Anaerobes	2 (4.8)	8 (9.8)	0.499
Bacteroides species	2 (4.9)	5 (6.1)	>0.99
Fusobacterium species	0 (0)	1 (1.2)	>0.99
Peptostreptococcus species	0 (0)	1 (1.2)	>0.99

ESBL = extended-spectrum beta-lactamase; KTR = kidney transplant recipient.

Less *K. pneumoniae* bacteremia in the KTR group may be related to less hepatobiliary infections in this group. Because *E. coli* is also the major pathogen of intra-abdominal infections, it is not surprising that a similar predominance of *E. coli* bacteremia was shown in both the KTR and control groups. It is interesting that none of the bacteremia episodes in the KTR group was attributed to BTIs. Although prophylactic cholecystectomy has been recommended in some countries in patients with asymptomatic cholelithiasis before kidney transplantation, the procedure is not performed in Taiwan.[23] The prevalence of cholelithiasis in the KTRs would be expected to be similar to that of the general population, and it is possible that the KTRs will develop BTIs later in their life as those with BTIs in the control group (mean age was 75 years).[24]

With regard to the consequences of bacteremia, the KTR group did not have increased mortality, a longer hospital stay, or a higher degree of renal function deterioration. Similar results were obtained upon comparing the non-elderly patient groups. In addition, the mortality rate in the KTR group is also numerically lower than that reported in two previous cohorts, which included nonelderly patients with community-onset bacteremia. Kollef et al reported a crude mortality rate of 4.1% in 415 American adults (mean age, 55 years) with community-acquired bacteremia[25], and

Table 5 Antimicrobial therapy and clinical outcome of the KTRs and the patients without kidney transplant (control) having community-onset bacteremia

Variables[a]	Number of cases (%)		*p*
	KTR group (n = 41)	Control group (n = 82)	
Initiation of effective drugs within 24 h	33 (80.5)	47 (69.5)	0.614
Discharge from the emergency department	4 (9.8)	7 (8.5)	>0.99
Admission to intensive care units	5/37 (13.5)	11/72 (15.3)	0.831
Hospital stay among survivors, d	6 (3–10)	11 (6–14)	0.020
Mortality			
In-hospital	1 (2.4)	10 (12.2)	0.172
At 28 d	1 (2.4)	10/76 (13.2)	0.100
At 12 mo	4/40 (10)	21/71 (29.6)	0.061

[a] Not all cases had the indicated information.
KTR = kidney transplant recipient.

Table 4 Antimicrobial susceptibility of selected drugs for specific bacteremic isolates from the KTRs and the patients without kidney transplant (control)

Drugs	All Enterobacteriaceae		*p*	Uropathogens		*p*
	Case number (%)			Case number (%)		
	KTR group (n = 29)	Control group (n = 55)		KTR group (n = 25)	Control group (n = 19)	
Cefazolin	19 (65.5)	39 (70.9)	0.827	17 (68)	15 (60)	0.749
Cefuroxime	21 (72.4)	43 (78.2)	0.827	18 (72)	15 (60)	0.843
CTX/CRO	27 (93.1)	48 (87.3)	0.846	24 (96)	15 (60)	0.663
Fluoroquinolones[a]	22 (75.9)	46 (83.6)	0.778	19 (76)	15 (60)	0.934
Gentamicin	21 (72.4)	42 (76.4)	0.880	17 (68)	15 (60)	0.749

[a] *Fluoroquinolones:* ciprofloxacin, levofloxacin, or lomefloxacin.
CRO = ceftriaxone; CTX = Cefotaxime; KTR = kidney transplant recipient.

in another Danish cohort of 851 persons aged 15—64 years there was a 30-day mortality rate of 11%.[26]

Younger age and fewer malignancies in the KTR group reflected the selection preference for transplantation candidates, and probably offset the adverse impact of immunosuppressants on the outcome of community-onset septicemia. A lower disease severity at initial presentation, which reasonably results from the health education offered by the transplantation team and less intra-abdominal infections, may be related to a lower hospital stay. Although the intervals between symptom onset and presentation did not differ between the two groups, the fact that a higher proportion (14.6%) of the control group presented with acute altered mental status would lead to underestimation of this parameter since these unconscious patients were sent to the ED immediately and their initial subjective symptoms were usually inaccessible.

This study had several limitations. A single-center setting limited its generalization of the study findings. The retrospective design may introduce classification errors owing to insufficient information, event documentation, or selection biases. Moreover, we did not evaluate the patients with community-onset bacteremia visiting outpatient clinics or other hospitals and this would underestimate the case numbers of community-onset bacteremia in the KTRs. Some differences in baseline characteristics in the two groups made any causal inference difficult. Further studies comparing KTRs with other age- and sex-matched controls are thus necessary. Last, some AKI patients may be undetected in the control group. The more sensitive criterion (0.3 mg/dL increase of serum creatinine within 48 hours) requires frequent blood samplings. The result that 50% of AKI patients in the KTR group and 25% in the control group fulfilled the aforementioned criterion reflected the fact that less frequent blood tests were performed for the patients in the control group.[14]

In conclusion, the KTRs with community-onset bacteremia had comparable clinical severity, antimicrobial susceptibility, and outcome to the control patients, despite different distribution of infection sources and pathogens. Our study indicates that the KTRs with community-onset bacteremia fare well, if they have access to medical care in time.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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