Erciyes Med J 2022; 44(5): 466–72 • DOI: 10.14744/etd.2022.63600
ORIGINAL ARTICLE – OPEN ACCESS

Bacterial Bloodstream Infection in Renal Transplant Recipients: 15 Years of Experience in a University Hospital

Nursel Çalık Başaran[1], Şehnaz Alp[2], Abdullah Tarık Aslan[3], Tural Pahsayev[3], Tolga Yıldırım[4], Şeref Rahmi Yılmaz[4], Oğuz Abdullah Uyaroğlu[1], Sevilay Karahan[5], Banu Sancak[6], Fazıl Tuncay Aki[7], Yunus Erdem[4], Gülşen Hasçelik[5], Serhat Ünal[2]

Cite this article as:
Çalık Başaran N, Alp Ş, Aslan AT, Pahsayev T, Yıldırım T, Yılmaz ŞR, et al. Bacterial Bloodstream Infection in Renal Transplant Recipients: 15 Years of Experience in a University Hospital. Erciyes Med J 2022; 44(5): 466-72.

A part of this study was presented as a poster in European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) between 21-24 April 2018, in Madrid, Spain

[1]Division of Genereal Internal Medicine, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [2]Department of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [3]Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [4]Division of Nephrology, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [5]Department of Medical Biostatistics, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [6]Department of Microbiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye; [7]Department of Urology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Submitted
28.12.2021

Accepted
16.02.2022

Available Online
09.06.2022

Correspondence
Nursel Çalık Başaran, Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of General Internal Medicine, Ankara, Türkiye
Phone: +90 312 305 30 29
e-mail: nurselcbasaran@gmail.com

ABSTRACT

Objective: The epidemiology of a bloodstream infection (BSI) in a renal transplant recipient (RTR) and the resistance profiles of the isolates provide important guidance for empirical treatment.

Materials and Methods: The medical records of RTRs from a single university hospital during the period of January 2000 to January 2016 were retrospectively evaluated for the presence of a BSI. Blood culture and antibiotic susceptibility results were reviewed in addition to demographic and clinical data. The distribution of causative microorganisms and risk factors for mortality in RTRs with a BSI were analyzed.

Results: In all, 74 BSIs and 76 distinct bacteria were observed in 56 (8%) of 702 RTRs. The mean age of the patients was 43±14 years; 55% were female, and 54% of the transplants were from living donors. Gram-negative bacteria, predominantly *Enterobacteriaceae*, were the most common (71%) pathogen. One-fifth of all BSIs occurred within the first month of transplantation. Among those that were Gram-positive, there were 5 coagulase-negative staphylococci and 8 *Staphylococcus aureus* BSIs. The rate of resistance to extended-spectrum β-lactamase, quinolone, and trimethoprim-sulfamethoxazole in Gram-negative enteric bacilli (GNEB) was 36%, 34%, and 50%, respectively. All of the GNEB were susceptible to carbapenems and amikacin. The overall mortality rate was 25%. The median length of time from the onset of BSI to death was 8 days (min–max: 2–46 days). The urinary tract was the primary source of infection in 53% of the patients. Delayed graft function significantly increased the mortality risk among RTR patients with a BSI.

Conclusion: Gram-negative bacteria were the leading cause of BSIs and demonstrated high resistance rates, and the most common site of infection was the urinary tract. Awareness of local epidemiology and resistance profiles will enable tailored treatment strategies to manage a BSI in RTRs.

Keywords: Bacteremia, bloodstream infections, Gram-negative bacteria, renal transplantation

INTRODUCTION

A bacterial bloodstream infection (BSI) is a serious complication and an important cause of mortality and morbidity in renal transplant recipients (RTRs) (1–6). A post-transplant BSI is associated with graft loss and decreased patient survival (7). Rapid initiation of appropriate empirical antibiotic therapy when there is a suspicion of bacteremia is of great importance; delays in therapy are related to poorer outcomes. However, the local epidemiological features have important implications for empirical therapy.

There are very few studies in the literature pertaining to the types and antimicrobial susceptibilities of microorganisms that lead to BSIs in RTRs. Furthermore, the spectrum of etiological agents and susceptibility profiles have changed over time and vary between centers (5–8).

The incidence of BSI in kidney transplantation varies between 7% and 25%, and is most often associated with a urinary tract infection (UTI) (37.8–55.2%), catheter-related infection (21%), or surgical wound infection (4%) (3–10). Drug-resistant ESKAPE pathogens (vancomycin-resistant *Enterococci* [VRE], methicillin-resistant *Staphylococcus aureus* [MRSA], extended-spectrum beta-lactamase [ESBL]-producing *Klebsiella pneumoniae* [*K. pneumoniae*], carbapenem-resistant *Pseudomonas aeruginosa* [*P. aeruginosa*], and ESBL-producing *Enterobacter* spp.) are found in 19.6% to 26.9% of BSI cases with high mortality (5–13).

This study was undertaken to (i) determine the incidence of a bacterial BSI in RTRs; (ii) investigate the demographic and clinical characteristics of patients with a BSI, (iii) define the species distribution and susceptibility profiles of the isolates that were observed between January 2000 and January 2016, and (iv) define risk factors for BSI mortality.

MATERIALS and METHODS

Ethical Considerations

The study protocol was approved by the Hacettepe University Ethics Committee on July 13, 2016 (no: GO 16/432).

Collection of Patient Data

This study was a retrospective, single-center, descriptive study. The data were collected from the hospital files and electronic medical records of RTRs who presented at a single hospital between January 1, 2000 and January 1, 2016 who had at least 1 positive blood culture result.

The demographic data of the patients, date of renal transplantation (RT), underlying renal disease, presence of comorbid illness, donor source (living vs cadaveric), presence of dialysis before transplantation, delayed graft function (defined as the need for hemodialysis within 1 week after transplantation), presence of corticosteroid use before transplantation, immunosuppressive treatment after transplantation, date of BSI, presence of central venous access, double-J stent, drainage catheter, and need for reoperation were recorded. In addition, details of the presence of any infection before transplantation, use of prophylactic antibiotics other than preoperative surgical prophylaxis, presence of acute/chronic rejection, duration of hospitalization, intensive care unit requirement, and the outcome of the infection episode were recorded and analyzed.

A positive blood culture result after transplantation was accepted as a BSI episode. In cases where the same pathogen was isolated in a subsequent blood culture during a single BSI episode, only the first isolate was included. Coagulase-negative staphylococci (CoNS) were considered a causative agent in the presence of ≥1 positive blood culture result with fever, hypothermia, or hypotension not due to other causes following the initiation of treatment. The white blood cell count; hemoglobin, serum creatinine, serum C-reactive protein, and procalcitonin values; and the erythrocyte sedimentation rate during the BSI episode were recorded. The results of other cultures performed were also reviewed to identify the source of the BSI, as well a review of the medical records for the presence of any clinical infection site.

The causative microorganisms identified were ESBL-producing *Escherichia coli* (*E. coli*), ESBL-producing *K. pneumoniae*, VRE, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *P. aeruginosa*, ESBL-producing *Enterobacter* spp., MRSA, and methicillin-resistant *Staphylococcus epidermidis*. Gram-negative *Enterobacteriaceae* were assumed to be multidrug-resistant (MDR) if there was resistance to ≥3 or more classes of antibiotics, extensively drug-resistant (XDR) if there was non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories (bacterial isolates remain susceptible to only 1 or 2 antimicrobial categories), or pan drug-resistant if there was non-susceptibility to all agents in all antimicrobial categories (14).

Septic shock was defined as a systolic blood pressure measurement of <90 mmHg that required vasoactive drug therapy. Biopsy-proven allograft rejections were recorded. At our center, the perioperative prophylaxis therapy was a single dose of cefazolin sodium administered 30 minutes before the skin incision. Trimethoprim-sulfamethoxazole (TMP-SMX) (double-strength tablet, 3 times a week) was administered for *Pneumocystis jirovecii* and UTI prophylaxis for 6 months, and oral valganciclovir was administered for Cytomegalovirus prophylaxis for 3 months in all patients beginning in 2010. Immunosuppressive drugs, such as calcineurin inhibitors, mycophenolic acid, and steroids, were administered according to the written protocols of the kidney transplant committee of our institution. Before the year 2009, the immunosuppressive regimens used were prednisolone plus mycophenolate or azathioprine plus tacrolimus or cyclosporine, whereas after 2009, prednisolone plus mycophenolate plus tacrolimus was used in all RTRs.

Microbiological Methods

The BD BACTEC 9240 Blood Culture System (Becton Dickinson & Co., BD Diagnostic Systems, Sparks, MD, USA) was used in routine practice at our institution during the study period. Blood cultures were incubated for 5 days. If the automated alert system signaled any growth in cultivated bottles, Gram-stained samples were examined microscopically to visualize the microorganism. Concomitantly, subcultures on blood and chocolate agar plates were performed and incubated at 35±2°C with 5–10% CO_2 for 48 hours. The final report result was defined as no growth if there were no colonies on the agar media.

Microbiological Identification and Susceptibility Results

Between 2000 and 2014, all isolates were identified using a BD Phoenix automated identification/susceptibility testing system (Becton Dickinson & Co., BD Diagnostic Systems, Sparks, MD, USA). Between January 2014 and November 2017, a VITEK MS V2 Myla Version 4.2 system (bioMérieux, Marcy-l'Étoile, France) was used. The antimicrobial susceptibility testing was performed using a VITEK 2 Compact system (bioMérieux, Marcy-l'Étoile, France). Resistant phenotypes were confirmed with either the Kirby-Bauer method or a gradient test (E-test; bioMérieux, Marcy-l'Étoile, France). The results of antimicrobial susceptibility tests were interpreted according to Clinical Laboratory Standard Institute guidelines between 2000 and 2017.

Statistical Analysis

The data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as number and percentage. The median (minimum–maximum) value was used for non-normally distributed numeric variables, and mean±SD for those with normal distribution. A chi-squared test was used to assess associations between categorical values in independent groups. The Mann-Whitney U test was used to compare continuous variables. Stepwise multivariate logistic regression analysis was used to determine risk factors affecting mortality. All of the statistical tests were 2-tailed, and the threshold of statistical significance was $p<0.05$.

RESULTS

In this study group, 56 (8%) of the 702 RTRs studied had at least 1 BSI episode. Among the 56, we recorded a total of 74 BSI episodes and 76 distinct bacteria. The mean age of the patients at the time of the BSI was 43±14 years, and 31 (55.4%) were female. In all, 54% had received a kidney from a living donor. The leading underlying causes of end-stage renal disease in RTRs who had a BSI episode were hypertension, diabetes, and glomerulonephritis. Nine of the 56 (16.07%) underwent retransplantation and 25 (44.6%) had biopsy-confirmed graft rejection before or after the BSI episode. The demographic characteristics of the RTRs with a BSI are provided in Tables 1 and 2.

Table 1. Demographic features of renal transplant recipients with bloodstream infections

	n	%
Total patient number, n	56	
Before 2010	45	80.3
Age at BSI, years (mean±SD)	43±14	
Female	31	55.4
Single transplant	47	84
Living donor	32	57.1
Dialysis, pretransplantation	54	96.4
Delayed graft function	14	25
Underlying cause of ESRD		
Hypertension	10	17.8
Diabetes mellitus	6	10.7
Glomerulonephritis	9	16
Amyloidosis	7	12.5
Pyelonephritis	1	1.7
Polycystic kidney disease	2	3.5
Uretero-vesical reflux	5	8.9
Solitary kidney	3	5.3
Nephrolithiasis	2	3.5
Unknown	11	19.6
Post-transplantation comorbidity		
Diabetes mellitus	11	19.6
Malignancy*	6	10.7
Biopsy-proven rejection	25	44.6
Mortality, in-hospital	14	56

*: Burkitt lymphoma, non-Hodgkin lymphoma, colorectal carcinoma, esophageal carcinoma, epidermoid carcinoma, basal cell carcinoma. BSI: Bloodstream infection; ESRD: End-stage renal disease

Table 2. Characteristics of renal transplant patients with a bloodstream infection

	n	%
Total BSI episodes	74	
Before 2010	63	
Number of BSI episodes		
1	44	78.6
2	9	16
>2	3	5.4
Laboratory values during BSI episode, median (min–max)		
Creatinine, serum, mg/dL	2.15 (0.6–12.8)	
Blood urea nitrogen, mg/dL	41 (12–139)	
Leukocyte, cells/mL	8 850 (8–25 000)	
Hemoglobin, g/dL	9.7 (6.8–14.7)	
Erythrocyte sedimentation rate, mm/h	36 (2–135)	
C-reactive protein, mg/dL	9.9 (0.28–61)	
Procalcitonin, mg/dL	10 (0.12–92)	
Propyhlactic antibiotic use, n (%)	10	13.5
Immunsuppresive regimen during BSI episode		
Mycophenolate	57	77.0
Corticosteroid	65	87.8
Tacrolimus	21	28.3
Cyclosporine	43	58.1
Azathioprine	34	45.9
Sirolimus	5	6.75
Double-J stent	21	28.3
Drainage catheter	16	21.6
Urinary catheter	14	18.9
Central venous catheter	38	51.3
Reoperation	3	4
Intensive care unit transfer	16	21.6
Time from transplantation to BSI		
First month	15	20.3
1–6 months	8	10.8
6–12 months	2	2.7
12–60 months	8	10.8
>60 months	41	55.4
Mortality during BSI episode		
First month	0	0
1–6 months	3	4.05
6–12 months	0	0
12–60 months	0	0
>60 months	11	14.86

BSI: Bloodstream infection

The median length of time from RT to first BSI was 56.3 months (min–max: 0.1–284 months). A BSI occurred within 30 days after transplantation in 20.3% and within 60 months in 44.6% (Table 2).

Since transplantation protocols regarding immunosuppressive and prophylactic antimicrobial usage both were revised at the study facility in 2010, data of the time from transplant to BSI episode among RTRs who underwent transplantation before and after 2010 were compared. The median time from transplant to first was 86 months (min–max: 0.1–284 months) in the patients who had a RT before 2010, and 0.6 months (min–max: 0.2–43.3 months) in the patients who had RT after 2010, which was a statistically significant difference (p=<0.001).

The overall mortality was 25% (14/56) among patients with RT, and 18.9% (14/74) of the BSI episodes resulted in mortality. The median time between the onset of BSI and death was 8 days (min–max: 2–46 days). The mortality rate during a BSI episode was 12% in the first year of transplantation and 22.4% after the first year of the transplantation, with no statistically significant difference (p=0.358). But the time between RT and BSI was statistically

Table 3. Results of univariate logistic regression analysis: risk factors for bloodstream infection mortality

Total RTR-BSI patients (n=56)	Survived (n=42)	Died (n=14)	p
Age at the time of BSI, years, median (min–max)	41.1 (20–65)	49 (39–70)	**<0.001**
Female, n (%)	24 (57.14)	7 (50)	0.877
Transplantation before 2010, n	32	13	0.39
Dialysis before transplantation, n	40	14	1.00
Delayed graft function, n	7	8	0.006
Live donor, n	24	8	1.00
Retransplantation, n	7	2	1.00
Diabetes mellitus, n	7	4	0.439
Hemoglobin, g/dL	9.75 (6.9–13.8)	9.7 (6.9–14.7)	0.161
White blood cell, µL	9500 (8–21 000)	7200 (400–25 000)	0.083
C-reactive protein, µL	1.5 (0–37)	2.6 (0–61)	0.556
ESR, mm/h	24.5 (0–112)	37 (0–135)	0.199
Procalcitonin, ng/mL	0 (0–66)	3.2 (0–92.3)	0.01
BUN, mg/dL	34 (13.8–122)	65.5 (18–139)	0.005
Creatinine, mg/dL	1.9 (0.7–12.8)	2.8 (0.6–7.8)	0.484
BSI episode count >1	7 /42	5/14	0.151
Time to first BSI (months)	35 (0.13–284)	124 (3–274)	0.001
Reoperation presence, n	3	1	1.0
Double-J stent presence, n	14	3	0.53
Drainage catheter presence, n	9	3	1.00
Urinary catheter presence, n	5	5	1.00
Central venous catheter, n	16	8	0.35
Prophylactic antibiotic, n	10	0	0.052
Resistant microorganism, n	13	6	0.518
Presence of rejection, n	15	9	0.119

BSI: Bloodstream infection; BUN: Blood urea nitrogen; ESR: Erythrocyte sedimentation rate; RTR: Renal transplant recipient

longer in patients who died than the patients who survived from BSI (median: 124 months, 35 months, respectively, p=0.001). A statistical comparison of the mortality rate during a BSI episode between patients who had transplantation before and after 2010 was not performed due to small number of cases after 2010. [13/45 (28.8%) before 2010 vs. 1/11 (9.1%) after 2010].

The age of the patient at the time of transplantation and BSI, the time between transplantation and BSI, and levels of serum procalcitonin and blood urea nitrogen (BUN) were found to be significant risk factors for mortality with BSI patients in univariate analysis (Table 3).

Multivariate logistic regression analysis indicated that delayed graft function was a significant risk factor for mortality in BSI-RTR patients (odds ratio [OR]: 16.6, confidence interval [CI]: 1.91–154.7). Higher serum erythrocyte sedimentation rate, serum procalcitonin, and serum BUN levels were related to mortality in BSI-RTR patients (OR: 1.04, 1.08, 1.04, respectively) (Table 4).

Concurrent culture results were evaluated to determine the primary source of the BSI. The distribution of the primary site of BSI is given in Figure 1. A UTI occurred in 39 episodes (52.7%) and was the leading cause of BSI. No infection site was detected in 18 (24.3%)

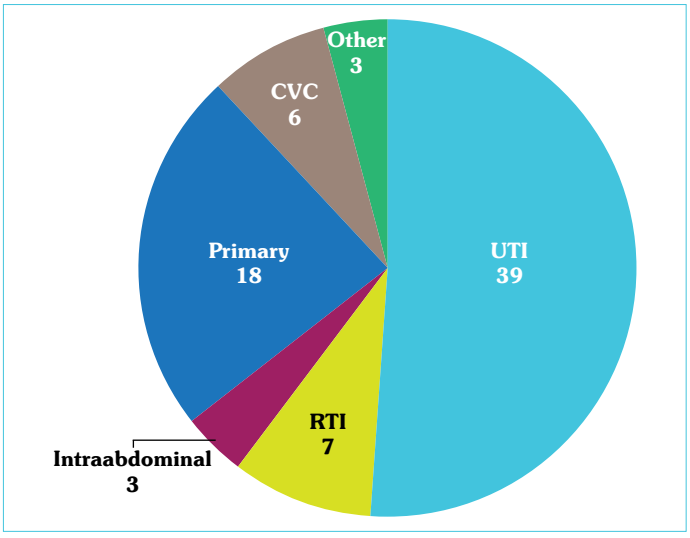

Figure 1. Primary site of bloodstream infection in renal transplant patients

BSI: Bloodstream infection; CVC: Central venous catheter; RTI: Respiratory tract infection; UTI: Urinary tract infection. Other: 2 instances of neutropenia, 1 instance of cellulitis

Table 4. Results of multivariate logistic regression analysis: risk factors for BSI mortality

	p	Standardized coefficients	CI 95% lower bound	CI 95% upper bound
Delayed graft function	0.013	16.64	1.791	154.735
ESR	0.014	1.07	1.009	1.085
Procalcitonin	0.011	1.08	1.018	1.150
BUN	0.054	1.04	0.999	1.087

CI: Confidence interval; BUN: Blood urea nitrogen; ESR: Erythrocyte sedimentation rate

episodes, which were considered a primary BSI. Pneumonia, acute pharyngitis, intra-abdominal abscess, febrile neutropenia, and cellulitis were other sources of BSI (Fig. 1).

The causative microorganisms of BSI are provided in Table 5 and Table 6. Throughout the study period, Gram-negative bacilli were the most frequently isolated pathogens in blood cultures (54/76, 71%), and the majority (44/54, 81%) were members of the *Enterobacteriaceae* family. ESBL production was positive in 16 (36.3%) of 44 GNEB cases, and the rate of quinolone and trimethoprim-sulfamethoxazole resistance was 15/44 (34%) and 22/44 (50%), respectively. The distribution of ESBL among GNEB cases did not significantly differ between 2000–2016 (p=0.30). Mortality was not significantly different between ESBL-positive (3/16) and ESBL-negative (3/28) BSI episodes (p=0.56).

While all GNEB were susceptible to carbapenems and amikacin, in 6 (14%) instances they were resistant to gentamicin. Three of 4 *Pseudomonas* isolate instances were *P. aeruginosa*, and 1 was classified as MDR. There were 3 *Acinetobacter* spp. observed, and 1 was considered XDR. Among all of the Gram-negative bacteria, 22 (40.7%) were classified as MDR.

The review of blood culture results revealed 51 CoNS isolates, but only 5 (all methicillin-resistant) were considered to be responsible for a BSI according to the criteria defined in the methods section. There was only 1 methicillin-resistant strain among 8 *Staphylococcus aureus* (*S. aureus*) isolates. Both of the *Enterococcus faecium* strains were resistant to ampicillin, while *Enterococcus faecalis* (n=2) isolates were susceptible, as expected. There was no evidence of vancomycin resistance in the *Enterococcus* spp.

E. coli isolates were highly resistant to amoxicillin-clavulanate (CAM) (73.3%) and 53.3% were resistant to TMP-SMX. Fluoroquinolone resistance was present in 40% of *E. coli* and 27.2% of *Klebsiella* isolates. Amikacin resistance was not observed in *E. coli* or *Klebsiella* isolates (Table 6). Carbapenem resistance was also not seen in those isolates.

Table 5. Microorganisms isolated in renal transplant recipients during bloodstream infection episodes

Microorganisms	n	%
Enteric: Gram-negative bacteria	**44**	**57.8**
Escherichia coli, total	30	39.4
Klebsiella spp., total	11	14.4
Other*	3	3.9
Non-fermentative: Gram-negative bacteria	**10**	**13.2**
Pseudomonas aeroginosa	4	5.3
Acinetobacter spp.	3	3.9
Other#	3	3.9
Gram-positive bacteria	**22**	**29**
Staphylococcus aureus	8	10.5
Coagulase-negative staphylococci	5	6.5
Streptococcus species	5	6.5
Enterococcus species	4	5.2
Total	**76**	**100**

*: 2 *Enterobacter* cloacae, 1 *Serratia marcescens*; #: 2 *Sphingomonas paucimobilis*, 1 *Stenotrophomonas maltophilia*

Table 6. Antibiotic resistance of *E. coli* and *Klebsiella* spp. in BSI episodes in RTR patients

	Resistance in *Escherichia coli*, Total number=30 n (%)	Resistance in *Klebsiella* spp, Total number=11
Amoxicillin-clavulonate	22 (73.3)	7 (63.6)
Trimethoprim sulfamethoxazole	16 (53.3)	4 (36.3)
Floroquinolones	12 (40)	3 (27.2)
Aminoglycosides		
Amikacin	0 (0)	0 (0)
Gentamycin	3 (10)	3 (27.2)
ESBL-positive	10 (33.3)	6 (54.5)

BSI: Bloodstream infection; ESBL: Extended-spectrum β-lactamase; RTR: Renal transplant recipient

DISCUSSION

We found that 8% of all RTRs had at least 1 BSI episode. There were 1.32 episodes per patient over a 15-year period in our university hospital. One-third of BSI episodes were within the first year after the transplantation. The overall in-hospital mortality in BSI episodes was 25%. Gram-negative microorganisms were seen in 71% of the episodes. *E. coli* was the leading cause of BSI, and ESBL was the major resistance problem among *Enterobacteriaceae*. The time from transplantation to BSI was significantly greater in patients who died than in those who survived (p=0.001). We found that delayed graft function was a predictive factor for mortality in RTRs who had a BSI.

Solid-organ transplantation can be a life-saving treatment for patients with organ failure, especially those with end-stage renal or liver disease. RT has been performed successfully for decades and provides improved quality of life and survival for thousands of patients with end-stage renal disease. There is, however, a considerable risk of infection, mostly due to the lifelong immunosuppressive treatment. BSIs are an important source of mortality in RTRs (1–6).

In this study, the findings of a BSI frequency of 8% among all RTRs and a BSI episode per patient rate of 1.32 were consistent with the literature. Siritip et al. (5) reported a BSI episode rate of 15.2% in 171 kidney transplant patients. A study of a cohort using data from the Spanish Network of Infection in Transplantation (RESITRA) noted a BSI incidence in RTRs of 7.2% and a BSI episode per patient rate of 1.2 (9). Shendi et al. (15) reported a BSI episode per patient rate of 1.33 in RTRs.

More than one-fifth of the BSI episodes occurred in the first month after transplantation, and nearly half were within 5 years of renal transplantation in our study group. In the Spanish cohort, nearly 60% of BSIs were in the first month after transplantation (9). Whereas Shendi et al. (15) reported that 55.2% of BSI episodes in RTRs were late-onset. Silva et al. (16) found that 62.2% of BSIs in RTRs occurred within 6 months of transplantation. This difference may be explained by the inclusion of some older RTRs who had undergone transplantation at another clinic and for whom we did not have information regarding the early transplantation period. Also, close monitoring in the early transplantation period, more attention to infection control measures, and prolonged antibacterial prophylaxis with TMP-SMX may have contributed to the lower rate of early-onset BSI in our study population. Prolonged immunosuppression over time may be another factor for late-onset BSI. In addition, 6 of our patients with BSI developed a malignancy, which can be associated with more severe immunosuppression.

We found that the overall in-hospital mortality of RTRs with BSI was 25%. The reported mortality rate due to a BSI varies between 8% and 25% in the literature (6, 9, 15, 16). This wide range may due to the design of the studies, the patient populations enrolled, and conditions at the centers where studies were conducted.

In our study population, we found that delayed graft function resulted in a nearly 16 times increased mortality risk among RTRs with a BSI. Silva et al. (16) reported that an Acute Physiology and Chronic Health Evaluation (APACHE) II score of ≥20, presence of shock at the time of diagnosis, and respiratory failure were independent risk factors for RTR-BSI mortality. Rojas et al. (17) demonstrated that a high Charlson comorbidity index score and persistent BSI were independent risk factors for mortality. In a Greek study, diabetes mellitus, septic shock, and *P. aeruginosa* infection were determined to be independent risk factors for poor outcomes of Gram-negative BSI episodes in RTRs (6).

As seen in the literature, the urinary tract was the most common source of BSI in RTRs, followed by respiratory tract infections, and central venous catheter-related infections. Shendi et al. (15) documented that more than half of the BSI episodes were due to a UTI. Silva et al. (16) reported that 37.8% of BSI in RTRs were due to a UTI and 18.4% were central venous catheter-related. Tsikala-Vafea et al. (6) reported that 70.9% of 195 Gram-negative BSI episodes in RTRs were secondary to a UTI. Preventing UTI infection, early recognition, and treatment of UTIs can prevent most BSI episodes in RTRs. Preventive strategies include infection control measures, shortening the duration of indwelling urinary catheters, and if present, ureteral stents. In our center, we have used a 6-month post-transplantation prophylactic antibiotic regimen since 2010.

Gram-negative microorganisms were seen in 71% of BSI episodes in RTRs. *E. coli* was the leading cause, and ESBL was the major resistance problem among *Enterobacteriaceae* (10/30 for *E. coli*; 6/11 for *Klebsiella*). Shendi et al. (15) reported ESBL in 12.7% of *E. coli* and 29.2% in *Klebsiella* spp.-associated BSI. In the RESITRA cohort, *E. coli* (30%), *P. aeruginosa* (14%), *Klebsiella* spp. (5%), *Enterobacter* spp. (4%), and *Acinetobacter baumannii* (3%) were the most common pathogens (9). Gram-positive bacteria were responsible for 30% of the BSI episodes: CoNS were the most frequently seen microorganisms, followed by *Enterococcus* spp. in 5% and *S. aureus* in 3% of the patients in the same study (9). The results of the Greek study indicated that *E. coli* was responsible for 63.7% of all Gram-negative BSI episodes in RTRs (6).

Among *E. coli* and *Klebsiella* isolates, no carbapenem resistance was seen in our study, and aminoglycoside resistance was extremely low. In the RESITRA study, third-generation cephalosporin-resistant enteric bacilli were responsible for 15.4% of BSIs in solid organ recipients (9). Shendi et al. (15) reported a 53.9% susceptibility to CAM, 47.2% to TMP-SMX, 97% to amikacin, and 66.7% to ciprofloxacin among community-acquired infections. Carbapenem resistance was not observed in their *E. coli* isolates. In the Greek study, 11.4% of *Enterobacteriaceae* infections were ESBL-positive and 5.42% were carbapenem-resistant (6).

The age of the patients at the time of the BSI episode was found to be related to mortality in univariate analysis. The median age at the time of a BSI was 43 years in our patient group. Hemmersbach-Miller et al. (18) compared RTR patients aged 40–60 years and >60 years of age for infection outcomes in the first year after transplantation and did not find any significant statistical difference.

One of the limitations of our study is the retrospective design; we did not have access to detailed information regarding the risk factors for BSI. Also, the inclusion of RTR-BSI patients who had undergone transplantation much earlier and outside of our clinic or country, our knowledge of the early post-transplantation period was minimal. However, these limitations had no direct effect on our results. We did not aim to identify the risk factors for BSI occurrence or protective factors or to analyze the outcomes of transplantation or surgery.

This is the first study to identify the BSI frequency, etiologic organisms, and resistance patterns among RTRs at our center, which has been a referral hospital for RT for many years and implements high-quality infection-control measures. Despite the emergence of highly resistant microorganisms all over the world, we had lower rates of MDR organisms in RTR-BSI patients.

CONCLUSION

The RTR patients who developed a BSI had a high mortality rate, and Gram-negative enteric bacteria were the most frequent microorganisms causing the infection. Special consideration should be given to RTRs with a BSI who require hemodialysis and those with higher serum procalcitonin, erythrocyte sedimentation rate, and BUN values due to a greater risk of mortality. Increasing resistance to pathogens will be a major problem for immunosuppressive patient groups. Prompt diagnosis and initiation of appropriate antibacterial therapies are important to saving renal grafts and saving lives. In order to develop treatment protocols, centers must know the microorganism distribution and resistance patterns. Further research is needed to evaluate the risk factors and mortality factors for BSI in RTR patients in the presence of changing treatment regimens and resistance factors.

Ethics Committee Approval: The Hacettepe University Clinical Research Ethics Committee granted approval for this study (date: 13.07.2016, number: GO 16/432).

Informed Consent: Due to the retrospective design, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NÇB, ŞA, TY, YE, SÜ; Design – NÇB, ŞA, TY, ŞRY; Supervision – BS, FTA, YE, GH, SÜ; Resource – ŞA, TY, NÇB, ATA, TP; Data Collection and/or Processing – NÇB, ŞA, TY, ATA, TP, BS, GH; Analysis and/or Interpretation – NÇB, SA, TY, ŞRY, FTA, YE, SÜ, SK; Literature Search – NÇB, ŞA, TY, OAU, SK, ŞRY, FTA; Writing – NÇB, ŞA, TY, SK, OAU, BS, GH, FTA, SÜ; Critical Reviews – YE, FTA, SÜ, YE, ŞRY, TY, ŞA.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Candel FJ, Grima E, Matesanz M, Cervera C, Soto G, Almela M, et al. Bacteremia and septic shock after solid-organ transplantation. Transplant Proc 2005; 37(9): 4097–9. [CrossRef]
2. Calik Basaran N, Ascioglu S. Epidemiology and management of healthcare-associated bloodstream infections in non-neutropenic immunosuppressed patients: a review of the literature. Ther Adv Infect Dis 2017; 4(6): 171–91. [CrossRef]
3. Møller DL, Sørensen SS, Perch M, Gustafsson F, Rezahosseini O, Knudsen AD, et al. Bacterial and fungal bloodstream infections in solid organ transplant recipients: results from a Danish cohort with nationwide follow-up. Clin Microbiol Infect 2022; 28(3): 391–7. [CrossRef]
4. Abdo-Cuza AA, Gómez-Bravo MA, Pérez-Bernal JB, Suárez-López J, Gómez-Peire F, Leiva-Torres JL, et al. Health Care-Associated Infection in Solid Organ Transplant Recipients. Transplant Proc 2020; 52(2): 509–11. [CrossRef]
5. Siritip N, Nongnuch A, Dajsakdipon T, Thongprayoon C, Cheungpasitporn W, Bruminhent J. Epidemiology, risk factors, and outcome of bloodstream ınfection within the first year after kidney transplantation. Am J Med Sci 2021; 361(3): 352–7. [CrossRef]
6. Tsikala-Vafea M, Basoulis D, Pavlopoulou I, Darema M, Deliolanis J, Daikos GL, et al. Bloodstream infections by gram-negative bacteria in kidney transplant patients: Incidence, risk factors, and outcome. Transpl Infect Dis 2020; 22(6): e13442. [CrossRef]
7. Cia CT, Li MJ, Li CW, Lee NY, Chang SS, Lee CC, et al. Community-onset bacteremia in kidney transplant recipients: The recipients fare well in terms of mortality and kidney injury. J Microbiol Immunol Infect 2016; 49(5): 685–91. [CrossRef]
8. Al-Hasan MN, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of Gram-negative bloodstream infection in solid organ transplant recipients. Am J Transplant 2009; 9(4): 835–43.
9. Moreno A, Cervera C, Gavaldá J, Rovira M, de la Cámara R, Jarque I, et al. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. Am J Transplant 2007; 7(11): 2579–86. [CrossRef]
10. Yeşilkaya A, Azap OK, Demirkaya MH, Ok MA, Arslan H, Akdur A. Bloodstream Infections among solid organ transplant recipients: Eight years' experience from a Turkish university hospital. Balkan Med J 2013; 30(3): 282–6. [CrossRef]
11. Daskalaki E, Koukoulaki M, Bakalis A, Papastamopoulos V, Belesiotuo E, Periveolioti E, et al. Blood stream infections in renal transplant recipients: A single-center study. Transplant Proc 2014; 46: 3191–3.
12. Bodro M, Sabé N, Tubau F, Lladó L, Baliellas C, Roca J, et al. Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. Transplantation 2013; 96(9): 843–9. [CrossRef]
13. Jackson KR, Motter JD, Bae S, Kernodle A, Long JJ, Werbel W, et al. Characterizing the landscape and impact of infections following kidney transplantation. Am J Transplant 2021; 21(1): 198–207. [CrossRef]
14. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18: 268–81. [CrossRef]
15. Shendi AM, Wallis G, Painter H, Harber M, Collier S. Epidemiology and impact of bloodstream infections among kidney transplant recipients: A retrospective single-center experience. Transpl Infect Dis 2018; 20(1): 1–9. [CrossRef]
16. Silva M Jr, Marra AR, Pereira CA, Medina-Pestana JO, Camargo LF. Bloodstream infection after kidney transplantation: epidemiology, microbiology, associated risk factors, and outcome. Transplantation 2010; 90(5): 581–7. [CrossRef]
17. Rojas L, Muñoz P, Kestler M, Arroyo D, Guembe M, Rodríguez-Créixems M, et al. Bloodstream infections in patients with kidney disease: risk factors for poor outcome and mortality. J Hosp Infect 2013; 85(3): 196–205. [CrossRef]
18. Hemmersbach-Miller M, Alexander BD, Sudan DL, Pieper C, Schmader KE. Infections after kidney transplantation. Does age matter? Clin Transplant 2019; 33(4): e13516. [CrossRef]