BLOODSTREAM INFECTIONS IN PATIENTS AFTER RENAL TRANSPLANTATION

Yavuz AYAR1, Alparslan ERSOY1, Sibel YORULMAZ2, Fatma Ezgi CAN3, Aysegul ORUC1, Abdulmecit YILDIZ1, Fatih YILDIRIM4, Akif DOGAN4, Halis AKALIN2

1Uludag University Faculty of Medicine, Internal Medicine, Department of Nephrology, Bursa

2Uludag University Faculty of Medicine; Department of Clinical Microbiology and Infectious Diseases, Bursa

3Uludag University, Department of Bioistatistics, Bursa

4Uludag University, Internal Medicine, Bursa

INTRODUCTION

Infections, particularly bloodstream infections, are one of the most significant morbidity and mortality causes following renal transplantation (1-5). In bloodstream infections which occurs following renal transplantation, urinary tract infection is one of the most important sources, and mostly gram-negative bacteria are isolated (6-12). Graft loss becomes an important issue following bacteremia, with an incidence of 25-50% (10-15). Thus, identification of risk factors and the appropriate treatment are significant for patient survival. The number of studies related to bacteremia following renal transplantation are limited in the literature. In this study, we retrospectively investigated renal transplant patients with bloodstream infections (BSIs), their clinical and laboratory characteristics, and risk factors for infections.

SUBJECTS AND METHODS

In this study, 95 patients (55 patients with bloodstream infections, 40 healthy as control group) medical records who underwent renal transplantation in our clinics between January 1st 2003 and December 31st 2013 were analyzed retrospectively. The clinical and laboratory characteristics of the patients following transplantation were evaluated. Among positive blood cultures, patients who met the Centers of Disease Control and Prevention's primary bloodstream infections diagnostic criteria which were updated in 2008 and secondary bloodstream infections were included into the study (16). Following operations, our patients received prophylactic trimethoprim-sulphamethoxazole (an average of 9-12 months) and valganciclovir (an average of 3 months).

BACTEC Plus (+) Aerobic/F (BD, Sparks, MD, USA) was used for blood culture. Sufficient blood to fill two to three bottles (8-10 ml per bottle) was drawn from different suitable veins. The blood cultures that gave positive signals were plated on 5% sheep-blood agar (BD BBLTM) and then incubated for 18-24 h at 350 C. The growing colonies that formed were transferred to an automatic identification panel (BD PhoenixTM PMIC/ID-70 and BD PhoenixTM NMIC/ID-99) to 0.5 McFarland turbidity. Panels were incubated in the PhoenixTM 100 BD system (BD, Sparks, MD, USA) and evaluated. We used Charlson Comorbidity Score and Pitt Bacteremia Score in our study and these scores were shown in table I and II. Systemic inflammatory response syndrome (SIRS) diagnosis was made with having at least two of the following criteria: a) body temperature >38oC or<360C, b) heart rate > 90/min, c) respiratory rate > 20/min or PaCO2< 32 mmHg, d) leukocyte (WBC) count >12000 or <4000 K/µL or >%10 shift to the left. Infections which occurred 48-72 hours after hospitalization or in 10 days after discharge were defined as nosocomial infections.

The urinary tract infection was defined as patient had either at least: (i) one of the following signs or symptoms: fever, urgency, frequency, dysuria, suprapubic tenderness and positive urine culture with ≥105 microrganisms/cm3; or (ii) two of the above signs or symptoms and one of the following: positive leukocyte esterase and/or nitrate, pyuria (≥10 WBC/mm3), or ≤ 105 microorganisms/cm3 if patient was on antibiotics (4). The definitions of Cytomegalovirus (CMV) infection and CMV disease were followed according to Canadian Transplantation Society Guidelines (17).

Statistical analysis

The suitability of the continuous variables to the normal distribution in groups was analyzed with Shapiro Wilk and Kolmogorov-Smirnov tests. Descriptive statistics for continuous variables of patients were provided as mean and standard deviation in parametric data, and as median and (minimum-maximum) in non-parametric data. Caterogical data were expressed as percentage (%) and frequency between groups. In the analyzes of continuous variables, Mann Whitney U test was used. In the analyzes of categorical data, Pearson Chi-Square test was used. For the analyzes of data, IBM SPSS version 22 (IBM Acquires SPSS Inc., Somers, NY, USA) program was used. In all statistical analyzes, p<0.05 value was accepted as statistically significant.

RESULTS

In this study, the mean age in the patient group was 47.16 ± 12.98, and 38.73 ± 10 in the control group (p<0.001). Sex distribution was similar in patients and controls (p=0.557). Mean Pitt Bacteremia Score was 0 (0-8), and mean Charlson Comorbidity Score was 2 (2-6) in the patients. Cadaveric transplants were more frequent in the patient group (74.5% versus 30%, p<0.001). Immunosuppressive treatment of the patients following transplantation was mostly cyclosporine (CsA) + mycophenolate mofetil (MMF) + prednisone (Pred) (50.9%), whereas in the control group, tacrolimus (Tac) + MMF + Pred were more frequent (50%) (p=0.262). In our renal transplant patients, bloodstream infections were developed mostly within the first 30 days (58.2%), and the mean duration to bloodstream infection after transplantation was 124 (1-3285) days.

38.2% of the patients had a stent in the ureter, 43.6% of the patients had central venous catheter (CVC) and these rates significantly higher when compared to control group (p<0.001 and p=0.015, respectively). The presence of lymphocele was not statistically different between two groups (p=0.646).

Following bloodstream infection, the incidence of acute rejection was 18.2% (p=0.004), and the incidence of chronic rejection was 12.7% (p=0.006). Graft loss was 38.2% in the patients following bloodstream infection and no graft loss was detected in control group (p<0.001). Early mortality (within the first 28 days) was higher as 12.7% in patients and there was no mortality in controls (p=0.020). When late mortality (after 28 days) rates were compared between two groups, it was significantly higher as 36.4% in the patients there was no mortality in controls (p<0.001). The clinical characteristics of the patients were summarized in Table III.

Nosocomial bloodstream infections were more frequent with a 80% rate. 50.9% of the patient group had no infection focus. Urinary tract infections (30.9%) and catheter-related BSIs (12.7%) were more frequently seen in the patient group. Mean CMV DNA level was 0 (0-35335) copy/ml in bloodstream infection cases, while it was 0 (0-5280) copy/ml in controls (p=0.015). Mean urea level was 110.15±60.18 mg/dL in BSI cases, while it was 53.58±14.54 mg/dL in controls (p<0.001). Mean creatinine level 2.69±1.92 mg/dL in patients, while it was 1.18±0.4 mg/dL in controls (p<0.001). E.coli (20%) and A.baumannii (20%) were most isolated bacteria in the blood culture. Totally, 61 bacteria were isolated in blood cultures, and 39 (64%) of them were gram negative. The BSI was polymicrobial in 8 of 55 patients (14.5%). Clinical, laboratory findings and blood culture results were summarized in Table IV and V

DISCUSSION

Renal transplantation is one of the most important treatment options in end stage renal disease. In particular, following cadaveric transplantation, infection-related complications are more seen (18, 19). In this study, the rate of those who underwent cadaveric transplantations was higher in the patients. In those who underwent cadaveric transplantations, the transport conditions of the organ, cold ischemia duration, immunosuppressive treatment, and acute rejection development may facilitate bloodstream infection development (20). The use of catheters, and the presence of a stent in ureter are also predisposes for infection development (21-23). The presence of lymphocele may trigger the development of infections; but this issue is controversial (24-26). In our study, the patients had significantly more CVC and stent in ureter compared to control group. There was no significant difference for the presence of lymphocele. Considering immunosuppressive treatments, Dantas et al. (27) evaluated 163 renal transplanted patients with BSI, and reported that cyclosporine (CsA) + azathiopurine (Azo) + prednisolone (Pred) combination was used in those who underwent live transplantation, and CsA + Azo + Pred was used in cadaveric cases. Between two groups, there was no difference in terms of BSIs development and immunsuppressive agents. In another study, CsA, Aza and Pred were used with 67%, 56.2%, and 97.8% rates, respectively; and there was also no difference between patient and control groups in terms of BSIs development and immunsuppressive agents (21). We also found no difference between two groups in terms of immunsuppressive regimens.

Following transplantation, the incidence of BSI is higher particularly within the first 6 months. Median time to BSIs was 235 day. 62% of BSIs were in the first 6 months after transplantation (21). Sacristan et al (22) observed 25.6% bacteremia in the first year. In Turkey, Yesilkaya et al (26) investigated 927 solid organ transplantation, and they detected early stage (first month) BSI in 15.3% of renal transplanted patients. In our study, 58.2% of BSIs was detected in the first 30 days.

Urinary tract infections are a frequent problem after kidney transplantation, and gram-negative rods such as E.coli are more isolated (9, 11, 12). Rojas et al (28) evaluated 155 renal transplanted patients, and reported that 23.2% of them had concomitant urinary tract infections. Al-Hasan et al (6) detected 72.9% urinary tract infections among BSI patients. In a study conducted in Spain, patients who had positive blood cultures after transplantation, there was 39% urinary tract infections (14). Silva and Sacristan et al (21, 22) detected 37.8% and 69.8% urinary tract infections in renal transplanted patients. In our study, the frequency of urinary tract infections was 30.9% in patients.

In previous studies, following renal transplantation, mostly gram-negative pathogens were isolated in BSIs. In a study conducted in Southern Spain, mostly E.coli was isolated in 474 renal transplanted patients (22). In a study conducted in Turkey, 67% gram-negative (36.69% E.coli, 1.59% A.baumannii) and 32% gram-positive (8% S.aureus) bacteria were detected in BSIs in patients following renal transplantation (26). Al-Hasan et al (6) also detected E.coli as 50% among gram-negative bacteria isolated in blood cultures. In different studies, gram-negative isolates were detected between 43-67% (21, 22, 26). In our study, gram-negative bacteria (E.coli and A.baumannii) were isolated mostly, similar to other studies.

Silva et al (21) detected 25.7% acute rejection in renal transplanted patients after BSIs. In another study, 13% acute rejection was reported after renal transplantation (14). In our study 18.2% acute rejection was developed after BSIs in renal transplanted patients.

BSIs are major cause of graft loss. It was reported that graft loss in patients with BSIs between 6.1-38.6% (21, 27). Graft loss was also high (38.2%) in our study. In different studies, Charlson comorbidity score was reported between 3 and 14 (21, 22, 28). In our study, mean Charlson comorbidity score in patients was 2 (2-6). These rates were lower in our study, and this might have been related to early initiation of treatment, antibiotic prophylaxis and less comorbidities. The early and late mortalities were found to be between 4.9-46% and 4-54% in BSIs patients (6, 14, 21, 25, 28). In our study, these rates were similar (12.7%, 36.4%).

In conclusion, BSIs following renal transplantation are a significant clinical problem for the graft and patient survival. Early detection and appropriate treatment of infections, and treatment and follow-up of acute rejection with caution are significant. Long term hospitalization and catheterization (ureteral stent, CVC) must be avoided.

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Table I: Charlson Comorbidity Score

Comorbidities	Scores
Myocardial Infarction	1
Congestive Heart Failure	1
Peripheral Vascular Disease	1
Cerebrovascular disease (without hemiplegia) TIA / CVA-without sequelae or minor sequelae	1
Dementia	1
COPD	1
Structural Connective Tissue Disease	1
Ulcer	1
Mild Liver Disease (chronic hepatitis, cirrhosis without PHT)	1
Diabetes (without end organ damage)	1
Diabetes (with end organ damage-nephropathy, retinopathy, neuropathy)	2
Hemiplegia	2
Moderate-Severe Renal Disease (serum creatinine >3mg/dL, dialysis, transplantation)	2
Second solid malignancy (without metastasis)	2
Leukemia; KML, KLL, AML, ALL, PV	2
Lymphoma; MM, NHL, HL,	2
Moderate Severe Liver Disease (cirrhosis+PHT+/- variceal bleeding)	3
Second solid malignancy (with metastasis)	6
AIDS	6
Age; For each decade of life after 40 age	1

Table II: Pitt Bacteremia Score

Criteria	Score
Fever (oral temperature)	
≤35^{0}C or ≥40^{0}C	2
35,1-36,0^{0}C or 39,0-39,9^{0}C	1
36,1-38,9^{0}C	0
Hypotension Decrease more of systolic pressure> 30 mmHg, diastolic blood pressure> 20 mm Hg or Systolic pressure <90 mmHg or Need to inotropic agents	2
Mechanical ventilation	2
Cardiac arrest	4
Mental status	
Awake	0
Disorientation	1
Stupor	2
Coma	4

Table III: Clinical characteristics of patient and control group

	Patient Group (n,%)	Control Group (n,%)
Age (year) (n)	47.16 ± 12.98	38.73 ± 10
Gender Female	18 (32.7%)	10 (25%)
Male	37 (67.3%)	30 (75%)
Transplantation type		
Live	14 (25.5%)	28 (70%)
Cadaveric	41 (74.5%)	12 (30%)
Immunosuppressive therapy	CsA + MMF + Pred 28 (50.9%) Tac + MMF + Pred 19 (34.5%) Other 8 (14.5%)	CsA + MMF + Pred 14 (35%) Tac + MMF + Pred 20 (50%) Other 6 (15%)
Duration to development of BSI after transplantation		
0-30 day	32 (58.2%)	
>30 day	23 (41.8%)	
Average time to BSI after transplantation (day)	124 (1-3285)	
Ureteral stent		
Yes	21 (38.2%)	0
None	34 (61.8%)	40 (100%)
Lymphocele		
Yes	13 (23.6%)	12 (30%)
None	42 (76.4%)	28 (70%)
Central venous catheter		
Yes	24 (43.6%)	7 (17.50%)
None	31 (56.4%)	33 (82.50%)
Acute rejection		
Yes	10 (18.2%)	0
None	45 (81.8%)	40 (100%)
Chronic rejection		
Yes	7 (12.7%)	0
None	48 (87.3%)	40 (100%)
Early mortality (≤28 day)		
Yes	7 (12.7%)	0
None	48 (87.3%)	40 (100%)
Late mortality (>28 day)		
Yes	20 (36.4%)	0
None	35 (63.6%)	40 (100%)

Table IV: Clinical and laboratory findings of patients and controls

	Patient Group
Fever (ºC)	37.9 ± 1.06
Pulse (minute)	96 (67-152)
Systolic arterial blood pressure (mmHg)	118.71 ± 19.01
Diastolic arterial blood pressure (mmHg)	72.98 ± 12.38
Hemoglobin (g/dL)	9.60 (4.80-15.70)
Leukocyte (K/µL)	8510 (130-31000)
Platelets (K/µL)	160000 (17000-926000)
INR	1.14 ± 0.23
CRP (mg/dL)	9.92 ± 6.96
PCT (ng/dL)	2.54 (0.10-200)
SIRS	
Yes	27 (49.09%)
None	28 (50.91%)
Pitt bacteremia score	0 (0-8)
Charlson comorbidity score	2 (2-6)
Type of infection	
Community-acquired	11 (20%)
Nosocomial	44 (80%)
Site of infection	
Urinary tract	17 (30.9%)
Pneumonia	1 (1.8%)
Catheter-related bloodstream infection	7 (12.7%)
Intraabdominal infection	1 (1.8%)
Cellulitis	1 (1.8%)
None (Primary bloodstream infection)	28 (50.9%)

INR: International normalized ratio. CRP: C reactive protein. PCT: Procalcitonin. SIRS: Systemic inflammatory response syndrome.

Table V: Blood culture results of the patients

Microorganism	Number of patients (%)
E.coli	11 (20%)
A.baumannii	11 (20%)
S.haemolyticus	5 (9.1%)
S.aureus	5 (9.1%)
S.epidermidis	5 (9.1%)
E.cloacae	4 (7.3%)
A.calcoaceticus complex	3 (5.4%)
K.pneumoniae	3 (5.4%)
E.faecium	3 (5.4%)
P.aeruginosa	3 (5.4%)
E.faecalis	2 (3.6%)
P.aeruginosa	2 (3.6%)
S.enteritidis	2 (3.6%)
S.maltophilia	2 (3.6%)
C.freundii	2 (3.6%)
S.hominis	1 (1.8%)
S.marcescens	1 (1.8%)
P.penneri	1 (1.8%)
P.vulgaris	1 (1.8%)
E.casseliflavus/gallinarum	1 (1.8%)
K.oxytoca	1 (1.8%)

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