Evaluation of extensively drug-resistant gram negative bacteremia among solid-organ transplant recipients: a multicenter study

Abstract

Background/aim: The aim of this study is to evaluate the distribution, sources, clinical features and mortality rates of bacteremia due to evaluation of extensively drug-resistant (XDR) gram negative among solid-organ transplant (SOT) recipients.

Materials and methods: A retrospective study of SOT recipients with bacteremia due to XDR gram negative pathogens in 11 centers between 2016 and 2018 was conducted. Patients records were evaluated.

Results: Of 171 bacteremia occurred in 164 SOT recipients 93 (56.7%) were liver, 46 (28%) kidney, 14 (8.5%) heart and 11 (6.7%) lung recipients. Bacteremia episodes were recorded in the first year in 63.7% of the patients (n = 109), early-onset bacteremia was recorded in 45% (n = 77) of the episodes. In multivariate analysis, catheter-associated bacteremia was an independent risk factor for 7-day mortality (p=0.037), and early-onset bacteremia was found as an independent risk factor for 30-day mortality (p = 0.017).

Conclusion: Difficult-to-treat infections due to XDR bacteria in SOT recipients shadow the success of transplantation. Central venous catheters seem to be the main risk factor. Judicious use of medical devices are of pivotal importance.

Key words: Solid-organ transplant recipients, drug-resistant, bacteremia

1. Introduction

Infections are still the most important cause of morbidity and mortality in solid-organ transplant (SOT) recipients despite advances in surgical techniques, immunosuppressive therapies and infection-control precautions. Transplant recipients are at risk for various

pathogens including opportunistic infections, reactivation of latent microorganisms, donor-mediated infections and healthcare-associated infections [1].

Bacteremia occurs in 5- 10% of kidney transplant and heart transplant recipients and more commonly in liver transplant and lung transplant recipients with rates of 10-25 %. The sources of bacteremia may include central-line catheters, the pulmonary tract, the urinary tract and the surgical site [2].

Significantly, recent reports have shown a shift towards gram negative bacteria (GNB) in the distribution of the pathogens that cause bloodstream infection (BSI) in the SOT recipients [3-6].

The incidence of GNB BSIs is reported to be 210.3/1000 person-years in the first month after transplantation and decreased to 25.7/1000 person-years between 2 and 12 months after transplantation [7]. The incidence of septic shock in patients who have gram-negative bacteremia is reported to be higher than in those with either gram-positive or fungal infections [8].

Growing antimicrobial resistance is another concern in SOT recipients. Frequent or prolonged hospitalization, exposure to multiple invasive procedures or to indwelling devices and the use of multiple antimicrobial drugs all put patients at high risk of colonization and infection with multiple drug resistant (MDR) bacteria. Managing infections caused by these pathogens is very difficult. Controlling MDR or extensively drug-resistant (XDR) bacteremia in immunosuppressive patients is a further challenge for clinicians. There is no specific prevention or treatment proposal.

The aim of this study is to evaluate the distribution of the etiological agents of XDR GNB BSIs and the clinical features of early- and late-onset XDR GNB BSIs along with 7- and 30-day mortality rates among SOT recipients.

2. Materials and methods

2.1. Data Collection

We conducted a retrospective study of SOT recipients of who had XDR GNB bacteremia in 11 centers (from Ankara, Malatya, Istanbul, Adana, Izmir, Denizli, Antalya) in Turkey between December 1, 2016 and December 31,2018. All patients were over 18 years of age.

Demographic, clinical and laboratory data were collected retrospectively from the patients' medical records and age, sex, type and date of transplant, date of BSI episode, microbiological characteristics, source of infection, laboratory tests and 7-day,30-day mortality rates were recorded.

Comorbidities included diabetes mellitus, cardiovascular diseases, chronic kidney disease, chronic liver disease and chronic pulmonary diseases.

This study was approved by the Baskent University Institutional Review Board (Project number: 94603339-604.01.02/20011).

The study evaluated demographic and microbiological characteristics, laboratory data, early- and late-onset XDR GNB BSI attacks, and 7- day,30-day mortality rates.

2.2. Definitions

Early-onset bacteremia: Bacteremia that develops within 30 days after transplantation

Late-onset bacteremia: Bacteremia that develops more than 30 days after transplantation

Extensively drug-resistant (XDR): Bacteria susceptible to only one or two antibiotics tested according to EUCAST criteria [9].

2.3. Statistical analysis

All categorical data were reported as number (percentage) or numeric data as mean±standard deviation or median (range). Categorical variables were compared using

Pearson's $\chi 2$ test. To determine the association between demographic/clinical variables and MDR GNB-related 7-and 30-day mortalities, all co-variables associated with a p value of <0.05 in the univariate analysis were selected for multivariate logistic regression analysis. The odds ratios (ORs) that had 95% confidence intervals (CIs) for the effect of the demographic and clinical predictors on mortality were evaluated using logistic regression.

The continuous numerical variables were not normally distributed, so they were presented as the median values compared using the Mann-Whitney U test. The categorical data were presented with frequency (%) and compared using a chi-square test.

3. Results

During the study period, 171 bacteremia episodes in 164 patients were recorded in 11 centers. Of these patients, 93 (56.7%) were liver, 46 (28%) were kidney, 14 (8.5%) were heart and 11 were (6.7%) lung recipients.

Of the 164 patients, 110 (67.3%) were male and the median age of all patients at the time of the bacteremia episode was 51 years (min. 19, max. 74). Table 1 shows the patients' demographic characteristics.

Hospitalization within the previous three months ranged from 0–7 times (median 1) and hospitalizations within the previous year ranged from 0–22 times (median 2).

Antibiotic use during the previous 30 days was recorded in 105 (61.4%) of the BSI episodes. In 57 of these cases (33.3%), multiple antibiotics were used. The distribution of the antibiotics previously used were carbapenems in 62 (36.5%), piperacillin-tazobactam in 21 (12.4%), cephalosporin in 20 (11.8%), glycopeptide in 19 (11.2%), linezolid in 15 (8.8%), colistin in 15 (8.8%) and quinolones in 12 (7.1%) patients.

Bacteremia episodes occurred in 63.7% of the patients (n = 109) in the first year after transplantation, 17.5% (n = 30) in the second year, 7% (n = 12) in the third year and 1.8% (n = 3) in the fourth year. The data showed a year-by-year decline. Early-onset bacteremia was found in 45% (n=77) of the episodes. Table 2 shows the clinical and microbiological characteristics of the attacks.

The distribution of isolated bacteria was as follows: 69 episodes (40.4%) Klebsiella pneumoniae, 59 (34.5%) Acinetobacter baumannii, 20 (11.7%) Escherichia coli, 18 (10.5%) Pseudomonas aeruginosa and 5 (2.9%) Enterobacter spp. In addition, 14 (8.2%) episodes were polymicrobial. The distribution of isolated bacteria according to transplanted organ presented in Table 3.

The sources of the bacteremia were as follows: 67 (39.2%) the surgical site, 40 (23.4%) urinary tract, 26 (15.2%) central-line catheters, 19 (11.1%) respiratory tract and 15 (8.8%) intra-abdominal collections. The source of the infection was not recorded in four patients. The distribution of bacteremia sources according to transplanted organ presented in Table 4.

The rate of 30-day mortality after bacteremia was 26.3% (n = 45), and 68.8% (31/45) of these deaths occurred within the first 7 days.

When we compared the data by the time of the bacteremia onset, the rate of early-onset bacteremia was higher in recipients of lung transplantation (81.8%,9/11) and heart transplantation (64.3%,9/14); the rate of late-onset bacteremia was higher in recipients of liver transplantation (58.2%,57/98) and kidney transplantation (62.5%, 30/48) (p=0.022). Transplantation from deceased donors was associated with an increased rate of early-onset bacteremia: 54.5% (42/79), while transplantation from living donors was associated with an increase in late-onset bacteremia: 60.6% (57/92) (p=0.048).

The evaluation of the data and laboratory values according to bacteremia time presented in Table 5 and Table 6.

The highest 7-day mortality rate was found in heart recipients as 50% (7/14), followed by lung recipients 36.4% (4/11), kidney recipients 16.7% (8/48), and liver recipients 12.2% (12/98). (p=0.002).

The 7-day mortality rate was 27.8% (22/79) for those receiving organs from deceased donors and 9.8% (9/92) for those receiving organs from living donors (p=0.002). The bacteremia in 15 (48.3%) of the 31 patients who died within 7 days was associated with a central-line catheter (p<0.001). The 7-day mortality rate was 26.7% (28/105) for patients who had used antibiotics for 30 days before the bacteremia attack and 4.5% (3/66) for those who had not (p<0.001). In early-onset bacteremia group, the 7-day mortality rate was 22.1% (17/77), while in late-onset bacteremia group was 14.8% (14/94) (p=0.225). In the multivariate analysis, only catheter-associated infection was found to be an independent risk factor (p=0.037) for 7-day mortality.

The highest 30-day mortality rate was 64.3% (9/14) in patients with heart transplants, followed by those with lung transplants (54.5%,6/11), renal transplants (22.9%,11/48), and liver transplants (19.4%,19/98) (p=0.001). The 30-day mortality rate was 39.2% (31/79) in transplant recipients from deceased donors and 15.2% (14/92) in transplant recipients from living donors (p< 0.001). The 30-day mortality rate was 20.7% (12/58) in patients without comorbidities, 23.3% (14/60) in patients with a single comorbidity and 35.8% (19/53) in patients with multiple comorbidities (p=0.157). When the 30-day mortality was evaluated by the source of the bacteremia, central-line catheters were responsible in 16 (35.5%) of the 46 patients (p< 0.001).

Of the 105 episodes of antibiotic use within the 30 days before the infection, 39 (37.1%) of these resulted in exitus ($p < 0.001$). The 30-day mortality rate was 33.8% (26/77) in cases of early-onset bacteremia and 20.2% (19/94) in cases of late-onset bacteremia ($p = 0.045$).

In the multivariate analysis, bacteremia seen in the first one month i.e. early-onset bacteremia was found as an independent risk factor for 30-day mortality ($p = 0.017$).

Table 7 shows the results of 7- and 30- day mortality univariate and multivariate analysis. The relationships between 7-day mortality rate and the median levels of leukocyte, CRP, and procalcitonin were statistically significant ($p = 0.013$, 0.003, and 0.019, respectively). The median levels of CRP and procalcitonin were higher in patients who experienced mortality within 30 days ($p = 0.003$ and 0.028, respectively). The laboratory values analysis of 7- and 30-day mortality presented in table 8.

4. Discussion

The increasing problem of antimicrobial resistance and the lack of new treatment options make it difficult to control infections. This is even more difficult for transplant patients. SOT recipients were admitted to the emergency department three times more frequently and were eighteen times more likely to be exposed to healthcare-associated infections [10]. The present study revealed hospitalization within the previous 3 months of BSI ranged from 0–7 times (median 1) and within the previous year of BSI ranged from 0–22 (median 2).

In the first two months after transplantation, there is a high risk of infection [11]. The present study, 63.7% of XDR GNB BSI occurred in the first year after transplantation. Patients are at the highest risk for MDR GNB infections in the early post-transplant

period because of the high dose of immunosuppressive drugs, the frequency of invasive procedures and the colonization of resistant bacteria. In the present study, there were more early post-transplant infections than late post-transplant ones and mortality was found to be higher in early-onset bacteremia than in late-onset.

The highest rate of early-onset bacteremia was in lung transplant patients and the lowest was in kidney transplant patients. The lack of chance of lung and heart transplant recipients other than deceased donors may also have contributed to the increased risk of infection. On the other hand, these results can be attributed to the fact that kidney transplants occur in the retroperitoneal region, necessitate shorter post-operative stays in intensive care units and are either less invasive procedures or shorter duration.

Antibiotic resistant pathogens are associated with healthcare environments and transplant patients frequently receive healthcare services. In the present study, catheter-associated XDR GNB BSIs were found to be an independent risk factor for 7-day mortality. This result emphasizes that catheters should be removed immediately in cases of catheter-associated infections. On the other hand, it also points out the importance of infection prevention measures in the insertion and maintenance of central-line catheters. Staff training and catheter-protection measures are recommended for this purpose [12].

The American Society of Transplantation Infectious Diseases Community MDR GNB Guideline reported mortality rates of 30–50% for carbapenem resistant Enterobacteriaceae, 40% for MDR P.aeruginosa, and greater than 52% for carbapenem resistant A.baumannii [11]. In our study we found a 7-day mortality rate of 18.1% and a 30-day mortality rate of 26.3%. The majority of patients in the present study had received liver transplants. The highest rates of 7- and 30-day mortality were in heart

transplant patients, followed by lung transplant patients. But the number of heart and lung transplants in our study is low.

The present study found high rates of late-onset bacteremia in recipients of transplants from living donors and high rates of early-onset bacteremia in recipients of transplants from deceased donors. Donor-type seemed to be effective in terms of bacteremia prognosis. Qiao et al. found that deceased donors were significantly related to mortalities from MDR GNB [3]. In the present study, the rates of 7- and 30-day mortality were higher in recipients of organs from deceased donors than in recipients of organs from living donors. Shields et al. evaluated infections by XDR A.baumannii in SOT recipients. They reported a 28-day clinical success rate of 49% in infected patients, but 44% of those patients had a recurrence within 3 months [13]. It's well known that achieving success in treatment of infections in transplant patients is difficult, but it becomes much more difficult with XDR bacteria. Because these patients are very fragile, when infection strikes, fast, and effective empirical antibiotic treatment should be provided, and the risk of recurrence should be kept in mind even when the infection is under control.

Studies have reported multiple and inappropriate uses of antibiotics as risk factors for MDR organisms [14]. In the present study, the use of antibiotics within 30 days before the BSI attack was significantly related to higher rates of both 7- and 30-day mortality, however after multivariate analysis it was not found as an independent risk factor. In transplant patients, hospitalization is generally preferred over outpatient treatment. Given this, while the patient's current episode of infection is being treated, the hospital environment may increase the chances of colonization or infection with resistant bacterial flora. Mazza et al. found mortality of 100% in patients with carbapenem-

resistant K. pneumoniae colonized before transplantation and mortality of 60% in patients colonized after transplantation [15].

The tendency to increase antimicrobial resistance among GNBs may affect local decisions regarding empirical antibiotic treatment of transplant patients who present with possible BSIs. Yeşilkaya et al. found that the XDR rate for A.baumannii was 38.9% [16]. Therefore, it is important to know the patient's colonization status in order to provide appropriate empirical antibiotic treatment rather than beginning inappropriate broad-spectrum antibiotics [17,18].

Limitations of this study are the lack of data on prospective follow up of patients, the effectiveness of the antibacterial treatments and the attributable mortality rates regarding bacteremia due to XDR GNB.

Infections -nowadays difficult-to-treat infections due to XDR bacteria- in SOT recipients shadow the success of transplantation. In this study, central venous catheters and antibiotic use seem to be the two main driving main risk factors for the development of difficult-to-treat bacteremia caused by XDR GNB. To combat these infections, judicious use of medical devices are of pivotal importance.

Acknowledgement/Disclaimers/Conflict of interest

All authors contributed to the study and accepted the final version of the article. The authors declare no conflict of interest. No funding was received for this study.

Informed consent

This study was approved by the Baskent University Institutional Review Board (Project number: 94603339-604.01.02/20011).

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Table 1. Clinical and demographic characteristics of patients

Characteristics	**Value**

Male/Female	110/54	
Median age	51 (min 19- max 74)	
The type of transplantation	**Patient**	**BSI Attack**
Liver	93 (56.7%)	98 (57.3%)
Kidney	46 (28%)	48 (28.1%)
Heart	14 (8.5%)	14 (8.2%)
Lung	11 (6.7%)	11 (6.4%)
The type of donor		
Living	88 (53.6%)	
Deceased	76 (46.3%)	
Comorbity		
None	57 (34.8%)	
One	59 (36%)	
Multiple	48 (29.3%)	
Hospitalization	Median value (range)	
Last 3 months	1 (min 0-max 7)	
Last 12 months	2 (min 0-max 22)	
BSI attack posttransplantation time		
0-12 months	109 (63.7%)	
13-24 months	30 (17.5%)	
25-36 months	12 (7%)	
37-48 months	3 (1.8%)	
49-60 months	5 (2.9%)	

≥61 months	12 (7%)
Antibiotic usage 30 days before BSI	
None	66 (38.9%)
Antibiotic usage	105 (61.4%)
One group antibiotic	47 (28.1%)
Multi groups antibiotics	57 (33.3%)

BSI: Bloodstream infection

Table 2. Clinical characteristics of the bacteremia episodes

İsolated bacteria	
Klebsiella pneumoniae	69 (40.4%)
Acinetobacter baumannii	59 (34.5%)
Escherichia coli	20 (11.7%)
Pseudomonas aeruginosa	18 (10.5%)
Enterobacter spp.	5 (2.9%)
Type of organism	
Monomicrobial	157 (91.8%)
Polymicrobial	14 (8.2%)
Site of primary infection	
Surgical site	67 (39.2%)
Urinary tract	40 (23.4%)
Catheter related	26 (15.2%)
Respiratory tract	19 (11.1 %)
Intra-abdominal	15 (8.8%)
Unknown	4 (2.3%)
Time of bacteremia onset	
Early-onset (≤30 days posttransplant)	77 (45%)
Late-onset (>30days posttransplant)	94 (55%)
Laboratory values	**mean± SD (min.- max.)**
Leucocyte (/µl)	11.411±8.200 (100- 43.900)
CRP (mg/L)	78.79±86.07 (1.82-467)
Procalsitonin (µg/L)	17.82±28.7 (0.08-100)

1 CRP: C-reactive protein, SD: standard deviation

Table 3. The distribution of isolated bacteria according to transplanted organ

Type of transplantation	**Most common**	**2nd most common**	**3rd most common**	**4th most common**
Liver (n=98)	*K.pneumoniae* (46.9%)	*A.baumannii* (40.8%)	*P.aeruginosa* (8.2%)	*E.coli* (4.1%)
Kidney (n=48)	*K.pneumoniae* (37.5%)	*E.coli* (25 %)	*A.baumannii* (18.8%)	*P.aeruginosa* (14.6%)
Heart (n=14)	*A.baumannii* (64.3%)	*E.coli* (21.4 %)	*K.pneumoniae* (7.1%)	*P.aeruginosa* (7.1%)
Lung (n=11)	*K.pneumoniae* (36.4%)	*Enterobacter spp.* (27.3%)	*P.aeruginosa* (18.2%)	*E.coli* (9.1%)

Table 4. The distribution of bacteremia sources according to transplanted organ

Type of transplantation	Most common	2nd most common	3rd most common	4th most common
Liver (n=98)	Surgical site (58.2%)	Respiratory (12.2%)	Urinary tract (12.2%)	Central-line catheter (9.2%)
Kidney (n=48)	Urinary tract (56.3%)	Surgical site (16.7%)	Central-line catheter (10.4%)	Respiratory (6.3%)
Heart (n=14)	Central-line catheter (50%)	Intra-abdominal collection (28.6%)	Respiratory (14.3%)	Urinary tract (7.1%)
Lung (n=11)	Central-line catheter (45.5%)	Respiratory (18.2%)	Surgical site (18.2%)	Intra-abdominal collection (18.2%)

Table 5. Evaluation of the datas according to bacteremia time

Risk factor	**Early-onset bacteremia n (%)**	**Late-onset bacteremia n (%)**	**p value**
The type of transplantation			**0.022**
Liver	41 (41.8)	57 (58.2)	0.331
Kidney	18 (37.5)	30 (62.5)	0.216
Heart	9 (64.3)	5 (35.7)	0.131
Lung	9 (81.8)	2 (18.2)	**0.011**
The type of donor			**0.048**
Decesead	42(54.5)	37 (39.4)	
Live	35 (45.5)	57 (60.6)	
Site of primary infection			0.663
Surgical site	33 (42.9)	34 (36.2)	0.373
Urinary tract	15 (19.5)	25 (26.6)	0.274
Catheter-related	13 (16.9)	13(13.8)	0.580
Respiratory	7 (9.1)	12(12.8)	0.447
Intra-abdominal	8 (10.4)	7 (7.4)	0.499
Isolated bacteria			0.783

A. baumanni	29 (37.7)	30 (31.9)	0.432
K. penumoniae	30 (39)	39 (41.5)	0.737
E. coli	7 (9.1)	13 (13.8)	0.337
P. aeruginosa	8 (10.4)	10 (10.6)	0.958
Enterobacter species	3 (3.9)	2 (2.1)	0.495
Polimicrobial	9 (11.7)	5 (5.3)	0.131

Table 6. Evaluation of the laborotory results according to bacteremia time

Laboratory values	**Early-onset bacteremia Median (min-max)**	**Late-onset bacteremia Median (min-max)**	**p value**
Leucocyte (/µl)	11100 (100-43900)	10800 (100-40040)	0.379
CRP (mg/L)	29.1 (1.85-320)	54 (1.82-467)	0.085
Procalsitonin (µg/L)	5.5 (0.1-100)	4.7 (0.08-100)	0.420

CRP: C-reactive protein

Table 7. Comparing the predictors of 7- and 30-day mortality

Risk factors	**7-days mortality**			**30-days mortality**		
	p value (univariate)	OR (%95Cl) (univariate)	Multivariate p value	p value (univariate)	OR (%95Cl) (univariate)	Multivariate p value
Gender	0.662	1.2 (0.530-2.718)		0.571	1.23 (0.600-2.523)	
Age	0.994	1.02 (0.971-1.032)		0.599	0.99 (0.967-1.019)	
The type of transplantation	**0.002**			**0.001**		
Liver	**0.021**	**2.522 (1.134-5.605)**	0.352	**0.017**	**2.300 (1.150-4.600)**	0.178
Kidney	0.757	1.15 (0.475-2.784)		0.528	1.285 (0.589-2.805)	
Heart	**0.001**	**0.180 (0.058-0.561)**	0.452	**0.001**	**0.165 (0.052-0.525)**	0.689
Lung	0.105	0.355 (0.097-1.299)		**0.028**	**0.269 (0.078-0.929)**	0.449
The type of donor	**0.002**	**3.559 (1.528-8.292)**	0.488	< **0.001**	**3.598 (1.740-7.439)**	0.593

Polimicrobial	0.290	0.519 (0.152-1.779)		**0.036**	**0.319 (0.105-0.968)**	0.790
Site of primary infection	**< 0.001**			**< 0.001**		
Surgical site	**0.012**	**3.217 (1.242-8.332)**	0.635	**0.002**	**3.412 (1.518-7.670)**	0.309
Urinary tract	**0.014**	**5.402 (1.229-23.743)**	0.309	**0.007**	**4.100 (1.369-12.280)**	0.163
Catheter-associated	**< 0.001**	**0.091 (0.036-0.232)**	**0.037**	**< 0.001**	**0.156 (0.064-0.380)**	0.398
Respiratory	0.326	0.578 (0.191-1.744)		0.269	0.571 (0.210-1.556)	
Intra-abdominal	0.844	0.875 (0.232-3.307)		**0.002**	**0.200 (0.067-0.600)**	0.301
Antibiotic usage 30 days before BSI	**< 0.001**	**0.131 (0.038-0.451)**	0.180	**< 0.001**	**0.169 (0.067-0.428)**	0.468
Bacteremi time	0.225	1.619 (0.740-3.541)		**0.045**	**2.012 (1.009-4.013)**	**0.017**

1 BSI: Bloodstream infection

2

3

Table 8. Comparing the laboratory values of 7-and 30-day mortality

	7-days mortality			**30-days mortality**		
	Yes	**No**		**Yes**	**No**	
Laboratory values	Median (min-max)	Median (min-max)	P value (univariate)	Median (min-max)	Median (min-max)	P value (univariate)
Leucocyte (/µl)	8650 (100-28600)	11000 (100-43900)	**0.013**	11000 (100-40040)	10900 (500-43900)	0.454
CRP (mg/L)	108.5 (3.49-467)	35 (1.8-320)	**0.003**	84.2 (1.85-467)	33.0 (1.82-320)	**0.003**
Procalsitonin (µg/L)	11.3 (1.0-86)	4.0 (0.08-100)	**0.019**	8.0 (0.4-100)	4.0 (0.08-100)	**0.028**

CRP: C-reactive protein