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

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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 that 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 is 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].

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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, İstanbul, Adana, İzmir, 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, and laboratory tests, and 7-day and 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 Başkent 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 and 30-day mortality rates.

2.2. Definitions

Early-onset bacteremia is defined as bacteremia that develops within 30 days after transplantation. Late-onset bacteremia is defined as bacteremia that develops more than 30 days after transplantation. Extensively drug-resistant (XDR) is defined as 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 covariables 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 to 7 times (median 1) and hospitalizations within the previous year ranged from 0 to 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%)

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%)	
Comorbidity		
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%)	
Multigroup antibiotics	57 (33.3%)	

BSI: Bloodstream infection

Enterobacter spp. In addition, 14 (8.2%) episodes were polymicrobial. The distribution of isolated bacteria according to transplanted organ is 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%) intraabdominal collections. The source of the infection was not recorded in four patients. The distribution of bacteremia sources according to transplanted organ is 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).

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 %)
Intraabdominal	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)
Procalcitonin (μg/L)	17.82 ± 28.7 (0.08–100)

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%)

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 is presented in Tables 5 and 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

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%)	Intraabdominal 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%)	Intraabdominal collection (18.2%)

Table 5. Evaluation of the data 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
Deceased	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
Intraabdominal	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
Polymicrobial	9 (11.7)	5 (5.3)	0.131

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

Table 6. Evaluation of the laboratory 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
Procalcitonin (μg/L)	5.5 (0.1–100)	4.7 (0.08–100)	0.420

CRP: C-reactive protein

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 analysis of laboratory values of 7- and 30-day mortality is 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 ranging from 0 to 7 times (median 1) and within the previous year of BSI ranging from 0 to 22 (median 2).

In the first 2 months after transplantation, there is a high risk of infection [11]. In 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 posttransplant 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 posttransplant infections than late posttransplant 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 postoperative stays in intensive care units, and are either less invasive procedures or require 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 the 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

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

Risk factors	7-day mortality			30-day 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
Polymicrobial	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)	
Intraabdominal	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
Bacteremia time	0.225	1.619 (0.740–3.541)		0.045	2.012 (1.009–4.013)	0.017

BSI: Bloodstream infection

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

	7-day mortality			30-day 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
Procalcitonin (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

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 is 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 is of pivotal importance.

Conflict of interest
The authors declare no conflicts of interest. No funding was received for this study.

Author contribution
All the authors contributed to the study and accepted the final version of the article.

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

References

1. Bartoletti M, Giannella M, Tedeschi S, Viale P. Multidrug-resistant bacterial infections in solid organ transplant candidates and recipients. Infectious Disease Clinics of North America 2018; 32 (3): 551-580. doi: 10.1016/j.idc.2018.04.004
2. Singh N, Limaye AP. Infections in solid-organ transplant recipients. In: Mandell GL, Bennett JE, Dolin R (editors). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Updated ed. Philadelphia, PA, USA: Churchill Livingstone; 2019. pp. 3440-3452
3. Qiao B, Wu J, Wan Q, Zhang S, Ye Q. Factors influencing mortality in abdominal solid organ transplant recipients with multidrug-resistant gram-negative bacteremia. BMC infectious diseases 2017; 17 (1): 171. doi: 10.1186/s12879-017-2276-1
4. Oriol I, Sabe N, Simonetti AF, Llado L, Manonelles A et al. Changing trends in the aetiology, treatment and outcomes of bloodstream infection occurring in the first year after solid organ transplantation: a single-centre prospective cohort study. Transplant International 2017; 30 (9): 903-913. doi: 10.1111/tri.12984
5. 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. Transplant Infectious Disease 2018; 20 (1). doi: 10.1111/tid.12815
6. Serefhanoğlu K, Timurkaynak F, Arslan H, Karakayalı H. Bacteremia among liver and kidney transplant recipients: etiologic agents and antimicrobial susceptibilities. Brazilian Journal of Infectious Diseases 2011; 15 (4): 408-409. doi: 10.1016/S1413-8670 (11)70218-5
7. Al-Hasan MN, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of gram-negative bloodstream infection in solid organ transplant recipients. American Journal of Transplantation 2009; 9 (4): 835-843. doi: 10.1111/j.1600-6143.2009.02559.x
8. Candel FJ, Grima E, Matesanz M, Cervera C, Soto G et al. Bacteremia and septic shock after solid-organ transplantation. Transplantation Proceedings 2005; 37 (9): 4097-4099. doi: 10.1016/j.transproceed.2005.09.181
9. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clinical Microbiology and Infection 2012; 18 (3): 268-281. doi: 10.1111/j.1469-0691.2011.03570.x

10. Timsit JF, Sonneville R, Kalil AC, Bassetti M, Ferrer R et al. Diagnostic and therapeutic approach to infectious diseases in solid organ transplant recipients. Intensive Care Medicine 2019; 45 (5): 573-591. doi: 10.1007/s00134-019-05597-y

11. Pouch SM, Patel G. Multidrug-resistant gram-negative bacterial infections in solid organ transplant recipients-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clinical Transplantation 2019; 33 (9): e13594. doi: 10.1111/ctr.13594

12. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J et al. Guidelines for the prevention of intravascular catheter-related infections. Clinical Infectious Diseases 2011; 52 (9): e162-193. doi: 10.1093/cid/cir257

13. Shields RK, Clancy CJ, Gillis LM, Kwak EJ, Silveira FP et al. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant Acinetobacter baumannii infections among solid organ transplant recipients. PloS one 2012; 7 (12): e52349. doi: 10.1371/journal.pone.0052349

14. Bodro M, Sabe N, Tubau F, Llado L, Baliellas C et al. Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. Transplantation 2013; 96 (9): 843-849. doi: 10.1097/TP.0b013e3182a049fd

15. Mazza E, Prosperi M, Panzeri MF, Limuti R, Nichelatti M, De Gasperi A. Carbapenem-resistant Klebsiella pneumoniae infections early after liver transplantation: a single-center experience. Transplantation proceedings 2017; 49 (4): 677-681. doi: 10.1016/j.transproceed.2017.02.028

16. 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 Medical Journal 2013; 30 (3): 282-286. doi: 10.5152/balkanmedj.2013.9256

17. Aguado JM, Silva JT, Fernandez-Ruiz M, Cordero E, Fortun J et al. Management of multidrug resistant gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. Transplantation Reviews 2018; 32 (1): 36-57. doi: 10.1016/j.trre.2017.07.001

18. Massa E, Michailidou E, Agapakis D, Papadopoulos S, Tholioti T et al. Colonization and infection with extensively drug resistant gram-negative bacteria in liver transplant recipients. Transplantation Proceedings 2019; 51 (2): 454-456. doi: 10.1016/j.transproceed.2019.01.076