Factors influencing mortality in solid organ transplant recipients with bloodstream infection

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Abstract

Although bloodstream infection (BSI) is a major cause of mortality after solid organ transplantation, information regarding its prognostic factors is scarce. To identify risk factors for 30-day mortality in solid organ transplant (SOT) recipients with BSI, we prospectively recorded all episodes of BSI occurring in adult SOT recipients from January 2007 to October 2014 at a university hospital. We identified 361 consecutive episodes of BSI involving 246 patients. The 30-day case-fatality rate from the onset of BSI was 11.4%. Factors independently associated with 30-day mortality in a logistic regression analysis were shock at presentation (OR 13.658; 95% CI 5.985–31.168), acute graft rejection in the previous 6 months (OR 3.681; 95% CI 1.059–12.795), and a platelet count of <50 000 × 10^9/L (OR 3.070; 95% CI 1.173–8.038). Kidney recipients were the patients with the best prognosis (OR 0.375; 95% CI 0.156–0.900). Our findings may help to identify SOT recipients with BSI who are at the highest risk of death.

Keywords: Acute graft rejection, antibiotic resistance, bloodstream infection, mortality, septic shock, solid organ transplantation
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Introduction

The number of cases of solid organ transplantation has risen dramatically in recent years, and, currently, solid organ transplantation extends the life-expectancy of >25 000 patients with end-stage organ diseases each year in the USA [1]. Nevertheless, the risk of infection after solid organ transplantation remains high, owing to the immunosuppressive treatment required to avoid graft rejection. Despite changes in immunosuppressive regimens and routine prophylaxis for infection, infectious diseases continue to constitute a major complication and the leading cause of morbidity and mortality among these patients, especially in the first month post-transplantation [2–4].

The management of bacterial infections in solid organ transplant (SOT) recipients is one of the most challenging clinical issues today [5]. In particular, bloodstream infection (BSI) is the most frequent life-threatening infectious complication after SOT [3,6]. Its incidence in the first 30 days ranges from 7.4% to 14%, depending on the type of transplant [3]. Significantly, recent studies have reported a shift in the distribution of the aetiology of BSI towards Gram-negative bacteria, especially multidrug-resistant (MDR) strains, as the predominant pathogens [6–8]. There has also been a sharp increase in the number of nosocomial-acquired infections, exposing SOT recipients to an increased risk of serious infections due to MDR pathogens, which are particularly difficult to treat [3]. Infections due to MDR organisms have also been associated with poor outcomes in some studies [4,8,9].

The management and prevention of bacterial infections in SOT recipients has become a key issue in modern

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transplantation [2]. The identification of prognostic factors associated with mortality that are amenable to medical intervention may well help to improve the outcomes of SOT recipients. However, current information about risk factors for mortality among these patients is scarce, and mainly derives from retrospective studies focusing on the mortality rates due to individual microorganisms.

The aim of this study was to determine the factors influencing mortality in a recent, large series of prospectively documented BSIs occurring in adult SOT recipients.

Materials and methods

Setting and study population

We conducted a prospective observational study at a tertiary university referral hospital in Barcelona, Spain, with an active transplantation programme (annual average of 104 kidney transplants, 50 liver transplants, and 15 heart transplants). From 1 January 2007 to 31 October 2014, all episodes of BSI occurring in hospitalized adult SOT recipients were included. Data regarding baseline characteristics, including immunosuppressive treatment, occurrence of acute allograft rejection and opportunistic infections, clinical features, microbiological studies, and outcomes, were carefully recorded in a specific database. For the purposes of this study, patients were divided into two groups according to their final outcome: survivors and non-survivors at 30 days from the onset of BSI. The two groups were compared to identify risk factors influencing mortality. The study was approved by the ethics committee of our institution.

At our hospital, the microbiology laboratory reports all positive results of blood cultures to the infectious disease team on a daily basis. All patients with BSI are visited by an infectious disease physician and followed up. Changes in antimicrobial treatment and general management are discussed when necessary.

Definitions

In accordance with the current standard definition, multidrug resistance was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [10]. BSI was considered to be nosocomial-acquired or community-acquired according to the criteria described previously [11]. Graft dysfunction before the onset of BSI was defined as follows: serum creatinine level of >1.5 mg/dL in kidney recipients; recurrence of hepatitis C virus, ischaemic cholangitis or cirrhosis in liver recipients; and history of heart failure in heart recipients. The BSI source was determined on the basis of clinical criteria, and isolation of any organism from a clinically significant site of infection matched with that obtained in blood cultures on the basis of the species identification and antibiotic susceptibility results. Catheter-related BSI was documented when the blood isolate was cultured from the catheter tip ($>10^3$ CFUs/mL). As the depth of infection was often difficult to determine, we combined surgical wound infections and abdominal organ/space infections into a single infectious source [12]. BSI was considered to be from a primary or unknown source in patients in whom no other BSI sites were identified.

Prior antibiotic therapy was defined as the receipt of any systemic antibiotic for $\geq$48 h in the previous month. Empirical antibiotic therapy was considered to be inadequate or inappropriate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism.

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, according to the International Guidelines of the Surviving Sepsis Campaign [13]. Acute allograft rejection was considered to be present when proven by biopsy, and 30-day mortality was defined as death from any cause within the first 30 days of the onset of BSI.

Antimicrobial prophylaxis

SOT patients received perioperative antibacterial prophylaxis for up to 48 h after transplantation. Specifically, kidney recipients received intravenous amoxycillin–clavulanate, and heart and liver recipients received intravenous vancomycin or teicoplanin plus aztreonam. Prophylaxis to prevent *Pneumocystis jiroveccii* infection with trimethoprim–sulphamethoxazole (a double-strength tablet taken once three times a week) was given in the first 6 months after transplantation. We used a prophylactic approach for those patients at high risk of cytomegalovirus disease [D^+/R^- patients, and patients who received antithymocyte globulin (ATG)]. In the other cases, we used a pre-emptive therapy approach [14]. We used *Candida* prophylaxis in high-risk liver transplant recipients. The antifungal administered was either fluconazole or an echinocandin, depending on the risk of drug interactions and toxicity. In heart recipients at high risk of invasive aspergillosis, we used intravenous amphotericin B (intravenous or nebulized) or an echinocandin [15].

Microbiological studies

Blood samples were processed with the BACTEC 9240 method (Becton-Dickinson Microbiology Systems, Sparks, MD, USA). The inoculated bottles were incubated for 5 days at 35°C before being discharged. Microbial identification was performed with commercially available panels (MicroScan (Siemens Healthcare Diagnosis Inc; West Sacramento, CA, USA) or Vitek (bioMérieux SA; Marcy-L'Etoile, France)), with standard

biochemical and/or enzymatic tests, or with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Daltonics; Bremen, Germany). CLSI criteria were used to define susceptibility or resistance to antimicrobial agents. Antibiotic susceptibility was tested with the microdilution method, following CLSI guidelines. The screening of MDR phenotypes, including methicillin-resistant *Staphylococcus aureus* ampicillin-resistant enterococci, extended-spectrum β-lactamase producers, and carbapenemase producers, was performed according to CLSI recommendations.

Statistical analysis

To compare patients for 30-day mortality, we used the chi-square test with continuity correction for categorical variables. Continuous data are presented as median (interquartile range (IQR)), and were analysed with the Mann–Whitney *U*-test. Multivariate conditional regression analysis of factors potentially associated with mortality was performed, including all statistically significant variables in the univariate analysis, sex and age, and all clinically important variables regardless of whether or not they were statistically significant. ORs and 95% CIs were calculated. The analysis was performed with the stepwise logistic regression model of SPSS version 18.0 (SPSS, Chicago, IL, USA). The survival curve was plotted with the Kaplan–Meier method. All statistical tests were two-tailed, and the threshold of statistical significance was $p < 0.05$.

Results

During the study period, 361 consecutive episodes of BSI were prospectively documented among 246 SOT recipients. Sixty-nine patients had more than one episode of BSI. The 30-day case-fatality rate was 11.4%. Sixty-one per cent of deaths (25/41) occurred within the first 7 days.

The median age of the subjects was 63 years (IQR 53–67 years). Seventy-two per cent of the episodes occurred in men, 60% were hospital-acquired, and 17% occurred in patients admitted to the intensive-care unit (ICU). Sixty-nine patients had more than one episode of BSI. The median time from transplantation to the onset of BSI was 222 days (IQR 31–2075 days). The most common source of infection was the urinary tract (37%), followed by the abdomen (25%) and catheters (16%). In 12% of the episodes, the source of infection was considered to be unknown. Causes of death of SOT recipients with BSI were shock/multiple organ failure (32 of 41 patients), respiratory failure (five of 41 patients), and acute hepatic insufficiency (four of 41 patients).

Table I shows the baseline characteristics of SOT recipients with BSI according to 30-day mortality. In the univariate analysis, liver recipients were more likely to have suffered a poor outcome, whereas kidney transplantation was associated with a lower mortality rate at 30 days. Table I also shows that nosocomial acquisition, admission to the ICU before the onset of BSI, the presence of acute graft rejection in the previous 6 months and the use of urinary and venous catheters were more frequent among non-survivors.

Patients with acute rejection within 6 months before the onset of BSI had only one episode of rejection. In the survivors group, six of seven patients showed a moderate degree of

TABLE I. Clinical characteristics of solid organ transplant recipients with bloodstream infection (BSI) according to 30-day mortality

Variables	Survivors (*N* = 320)	Non-survivors (*N* = 41)	p
Male sex, *n* (%)	228 (71.3)	31 (75.6)	0.689
Age (years), median (IQR)	63 (56–67)	60 (53–65)	0.194
Underlying diseases, *n* (%)	268 (83.8)	32 (78.0)	0.487
Renal impairment[a]	28 (8.8)	7 (17.1)	0.157
Diabetes mellitus	80 (25.2)	8 (19.5)	0.564
Heart disease	61 (19.1)	7 (17.1)	0.925
COPD	23 (7.2)	5 (12.2)	0.413
Haematological disorders	9 (2.8)	4 (9.8)	0.072
Solid tumour	15 (4.7)	1 (2.4)	0.798
Other	106 (33)	10 (24.4)	0.342
Type of transplant, *n* (%)			
Kidney	179 (55.9)	9 (22.0)	<0.001
Liver	95 (29.7)	22 (53.7)	0.004
Heart	43 (13.4)	8 (19.5)	0.416
Multi-organ	3 (0.9)	1 (2.4)	0.942
Prior transplant, *n* (%)	20 (6.3)	2 (4.9)	1
Immunosuppressive regimens, *n* (%)			
Prednisone	241 (75.3)	31 (75.6)	1
Tacrolimus	19 (5.9)	6 (14.6)	0.082
Cyclosporine A	23 (7.2)	4 (9.8)	0.785
Mycophenolate mofetil	13 (4.1)	4 (9.8)	0.219
mTOR inhibitors	13 (4.1)	2 (4.9)	1
Tacrolimus + mycophenolate mofetil	159 (49.7)	14 (34.1)	0.087
Cyclosporine A + mycophenolate mofetil	68 (21.3)	7 (17.1)	0.677
mTOR inhibitors + mycophenolate mofetil	30 (9.4)	0	0.081
Tacrolimus + mTOR inhibitors	5 (1.6)	1 (2.4)	1
Lymphocyte-depleting antibody at transplant	141 (44.1)	22 (53.7)	0.319
OKT3/ATG (6 months)	24 (7.5)	2 (4.9)	0.771
Receipt of more than one pulse of 1 g of intravenous methylprednisolone (6 months)	35 (10.9)	6 (15.0)	0.618
Graft dysfunction before the onset of BSI[b], *n* (%)	58 (18.1)	18 (43.9)	<0.001
Nosocomial acquisition, *n* (%)	183 (57.2)	32 (78.0)	0.017
ICU stay at the onset of BSI, *n* (%)	46 (14.4)	17 (41.5)	<0.001
Acute allograft rejection within the preceding 6 months, *n* (%)	18 (5.6)	7 (17.1)	0.017
Prior antibiotic therapy[c], *n* (%)	209 (65.7)	32 (78.0)	0.160
TMP–SMZ prophylaxis, *n* (%)	75 (23.4)	14 (34.1)	0.192
Use of urinary catheter, *n* (%)	107 (33.4)	23 (56.1)	0.008
Use of venous catheter, *n* (%)	153 (47.8)	30 (73.2)	0.004
Median days from transplantation (IQR)	222 (31–2187)	263 (41–1580)	0.952
≤30 days from transplantation, *n* (%)	79 (24.7)	4 (9.8)	0.052
≤90 days from transplantation, *n* (%)	124 (38.8)	15 (36.6)	0.922

ATG, antithymocyte globulin; COPD, chronic obstructive pulmonary disease; ICU, intensive-care unit; IQR, interquartile range; mTOR, mammalian target of rapamycin; TMP–SMZ, trimethoprim–sulphamethoxazole.
[a]Renal impairment was defined as a serum creatinine level of >1.5 mg/dL.
[b]Graft dysfunction before the onset of BSI was defined as follows: serum creatinine level of >1.5 mg/dL in kidney recipients; recurrence of hepatitis C virus, ischaemic cholangitis or cirrhosis in liver recipients; history of heart failure in heart recipients.
[c]Prior antibiotic therapy was defined as the receipt of any systemic antibiotic in the preceding month.

rejection according to histopathology. The other one showed a severe degree of rejection. All of these patients were treated with a bolus of steroids. In the non-survivors group, 13 of 15 patients showed a moderate degree of rejection, one patient showed borderline rejection, and one patient showed a severe degree of rejection. Seven of the patients had been treated with a bolus of steroids, three had been treated with a bolus of steroids plus ATG, three had been treated only with ATG, and one had been treated with plasmapheresis and intravenous immunoglobulins; the patient with borderline rejection had been treated with increased doses of the immunosuppressive drugs.

Table 2 shows the clinical and laboratory findings at the onset of BSI according to 30-day mortality. Shock at presentation, renal impairment and concomitant infection due to cytomegalovirus were more frequent among non-survivors. Regarding the laboratory findings, non-survivors had lower levels of serum albumin and lower blood counts of leukocytes, neutrophils, lymphocytes and platelets than survivors.

Table 3 shows the causative pathogens isolated in each episode of BSI according to 30-day mortality. Seventy-two per cent of monomicrobial BSIs were due to Gram-negative bacilli (GNB). GNB showed a high rate of resistance to major antibiotics (33.3% of them were MDR and 14.5% were carbapenem-resistant). Carbapenem resistance was more frequent among non-survivors, accounting for 42% of the isolates. No episodes with vancomycin-resistant *Enterococcus faecium* were found. The frequency of MRSA bacteraemia was also low.

After application of a backward stepwise logistic regression model (Table 4), septic shock at presentation (OR 13.658; 95% CI 5.985–31.168), the presence of acute graft rejection in the previous 6 months (OR 3.681; 95% CI 1.059–12.795) and a platelet count of <50 000 × 10^9/L (OR 3.070; 95% CI 1.173–8.038) were found to be risk factors for 30-day mortality of SOT recipients with BSI. Kidney transplantation (OR 0.375; 95% CI 0.156–0.900) was associated with the best prognosis.

TABLE 2. Clinical and laboratory findings at the onset of bloodstream infection according to 30-day mortality

Variables	Survivors (*N* = 320)	Non-survivors (*N* = 41)	p
Clinical presentation, *n* (%)			
Septic shock at presentation[a]	34 (10.6)	29 (70.7)	<0.001
Renal impairment[b]	111 (34.7)	29 (70.7)	<0.001
ICU admission	68 (21.3)	29 (70.7)	<0.001
Inadequate empirical antibiotic therapy[c]	88 (28.1)	14 (36.8)	0.353
Concomitant CMV	32 (10.0)	9 (22.0)	0.045
Laboratory findings, *n* (%)			
Platelet count of <50 000/mm^3	17 (5.3)	15 (36.6)	<0.001
Lymphocyte count of <500/mm^3	130 (40.6)	24 (58.5)	0.044
Neutrophil count of <1000/mm^3	10 (3.1)	5 (12.2)	0.020
White blood cell count of <5000/mm^3	67 (20.9)	17 (41.5)	0.006
Hypoalbuminaemia[d]	175 (54.7)	34 (82.9)	0.001

CMV, cytomegalovirus; ICU, intensive-care unit.
[a]Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation.
[b]Renal impairment was defined as a serum creatinine level of >1.5 mg/dL.
[c]Empirical antibiotic therapy was considered to be inadequate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism.
[d]Hypoalbuminaemia was defined as a serum albumin level of < 3g/L.

TABLE 3. Causative pathogens isolated in each episode of bloodstream infection (BSI) according to 30-day mortality

Causative organisms	Survivors (*N* = 320)	Non-survivors (*N* = 41)	p
Monomicrobial BSI, *n* (%)	282 (88.1)	35 (85.4)	0.612
Gram-positive bacteria	69 (24.5)	13 (37.1)	0.106
CNS	18 (6.4)	5 (14.3)	0.155
MSSA	15 (5.3)	0	0.388
MRSA	3 (1.1)	1 (2.9)	0.375
Enterococcus faecalis	12 (4.3)	2 (5.7)	0.659
Enterococcus faecium	8 (2.8)	3 (8.6)	0.110
Streptococcus pneumoniae	7 (2.5)	1 (2.9)	1
Listeria monocytogenes	3 (1.1)	0	1
Other	3 (1.1)	1 (2.9)	0.375
GNB	209 (74.1)	19 (54.3)	0.014
Escherichia coli	99 (35.1)	6 (17.1)	0.033
Klebsiella pneumoniae	47 (16.7)	1 (2.9)	0.057
Enterobacter species	13 (4.6)	0	0.375
Serratia marcescens	3 (1.1)	0	1
Morganella morganii	3 (1.1)	0	1
Salmonella enteritidis	2 (0.7)	0	1
Pseudomonas aeruginosa	27 (9.6)	8 (22.9)	0.039
Acinetobacter baumanii	3 (1.1)	1 (2.9)	0.375
Stenotrophomonas maltophilia	0	1 (2.9)	0.110
Other GNB	5 (1.8)	1 (2.9)	0.507
Bacteroides fragilis	3 (1.1)	1 (2.9)	0.445
Other	3 (1.1)	0	1
MDR Gram-negative bacilli	67 (23.8)	9 (25.7)	0.798
ESBL-producing *Enterobacteriaceae*	32 (11.3)	2 (5.7)	0.584
Carbapenem-resistant GNB	25 (8.9)	8 (22.9)	0.018
Yeast	4 (1.4)	3 (8.6)	0.032
Candida albicans	4 (1.4)	0	1
Candida non-*albicans*	0	3 (8.6)	<0.001
Polymicrobial, *n* (%)	38 (11.9)	6 (14.6)	0.612

CNS, coagulase-negative staphylococci; ESBL, extended-spectrum β-lactamase; GNB, Gram-negative bacilli; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Discussion

Septic shock at presentation, the presence of acute graft rejection in the previous 6 months and a platelet count of <50 000 × 10^9/L were the only factors that were independently

TABLE 4. Independent risk factors for 30-day mortality in solid organ transplant recipients with bloodstream infection

Variables	OR (95% CI)	p
Septic shock at presentation[a]	13.658 (5.985–31.168)	<0.001
Acute graft rejection within the preceding 6 months	3.681 (1.059–12.795)	0.040
Platelet count of <50 000/mm^3	3.070 (1.173–8.038)	0.022
Kidney recipients	0.375 (0.156–0.900)	0.028

[a]Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation.

associated with 30-day mortality among SOT recipients with BSI. Kidney transplantation was related to better prognosis.

Septic shock is the most severe complication in the context of BSI in SOT recipients and in the general population [4,16]. Improving the management of septic shock remains a great challenge. Numerous therapeutic strategies aimed at reducing mortality in this group of critically ill patients, including therapies to modulate and downregulate the complex network of sepsis-induced inflammatory and coagulopathy processes, have been studied. However, most studies have not shown significant reductions in mortality [17,18]. The latest guidelines of the Surviving Sepsis Campaign recommend protocolized resuscitation with intravenous fluids and early empirical antibiotic therapy [13], similarly to other meta-analyses [19,20], as measures to reduce mortality in severe sepsis.

An intriguing and novel finding from the current investigation is the independent association of the presence of acute graft rejection in the previous 6 months and mortality in patients with BSI. At present, little is known about the relationship between sepsis and graft rejection. Nevertheless, two recent retrospective analyses found that acute graft rejection was an independent risk factor for urinary tract infection in kidney recipients [21,22]. Moreover, in a prospective study, acute graft rejection was associated with BSI due to MDR GNB [6]. In histological terms, acute rejection is observed as an inflammatory response of the host to the transplanted organ, excluding the mechanisms that resulted in the native graft disease [23]. Treatment modalities for acute rejection generally entail augmentation of immunosuppressive strategies. It might be speculated that the key is to find the dose of immunosuppressants that minimizes the risk of rejection without causing a significant increase in the risk of infection.

Thrombocytopenia is frequently observed in critically ill patients, and it has been associated with reduced survival rates in general ICU populations with or without infections [24,25]. Our study suggests that a platelet count of $<50\ 000 \times 10^9$/L is a risk factor for mortality in SOT recipients with BSI. A highly significant correlation between platelet count and platelet adhesion to all leukocyte subpopulations has been described. The exact mechanisms of this interaction in sepsis are not clearly understood, although there is increasing evidence that they play an important role in the development of multiple organ failure and disseminated intravascular coagulation [26]. A lower platelet count has previously been identified as an unadjusted risk factor for mortality in some retrospective studies in SOT recipients with BSI [27,28].

In our study, kidney recipients with BSI had a lower mortality rate than other organ recipients. This is probably because kidney recipients are much more likely than the other recipients to have a urinary source of infection, undergo surgical manipulation, present with chronic local inflammation, and require prosthetic devices [3,29]. Moreover, it is well known that BSI from a urinary source is usually associated with a better outcome than BSI from other sources [30].

We did not find an association between inadequate empirical antibiotic therapy and poorer outcome. However, in our study, the median onset of targeted antimicrobial therapy among those patients initially receiving an inadequate empirical treatment was <24 h. It can be speculated that a short delay in receiving appropriate antimicrobial therapy does not necessarily lead to an adverse outcome in SOT recipients. Moreover, a recent study [31] showed that the mortality rate was lower among SOT recipients than among non-transplant patients with bacteraemia, suggesting that the immunosuppression associated with transplantation may provide a survival advantage to transplant recipients with sepsis through modulation of the inflammatory response.

Our study has some limitations that should be noted. First, it is a single-centre study, and our findings may be attributable to institution-specific variables, and may not reflect the epidemiology of different centres and/or geographical areas. Second, we did not have information regarding previous patient colonization and nutritional status. Finally, we analysed a heterogeneous group of SOT recipients who may have had their own specific risk factors for mortality.

In conclusion, this prospective study involving a large number of SOT recipients with BSI has shown that shock at presentation, previous acute graft rejection and a platelet count of $<50\ 000 \times 10^9$/L are independent risk factors for mortality in SOT recipients with BSI. Kidney transplantation was associated with a better prognosis. Further research is warranted to improve preventive procedures, general measures and antibiotic therapy for BSI in this population of patients. Moreover, the relationship between acute rejection and mortality should be specifically examined in further studies.

Transparency declaration

The authors of this manuscript have no conflicts of interest related to the material presented.

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