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ARTICLE

Statins are associated with improved outcomes of bloodstream infection in solid-organ transplant recipients

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Abstract Among recipients of intra-abdominal solid-organ transplants, bloodstream infections (BSIs) are a major cause of mortality. We undertook a retrospective cohort study of recipients of kidney, pancreas, and/or liver transplants with BSIs at a single center over an 11-year period. Multivariate analysis using logistic regression was used to determine independent predictors of 15-day mortality and clinical cure, with a focus on the use of statins. Three hundred and eleven recipients of solid-organ transplants had 604 episodes of BSI. Forty-four (14%) died within 15 days of BSI. Sixteen percent did not achieve clinical cure. In the multivariate model, each one point increase in the APACHE score was associated with a 1.09-fold increased risk of death (95% confidence interval [CI] 1.00–1.18, P=0.03). The lack of appropriate antibiotic therapy was associated with a four-fold higher risk of death within 15 days (odds ratio [OR] 4.65, 95% CI 1.46–14.78, P=0.009). Statin use was protective (OR 0.18, 95% CI 0.04–0.78). Patients with high APACHE scores, nosocomial rather than community source of BSI, lack of appropriate antibiotic therapy, and mental status changes were less likely to achieve clinical cure of their BSIs. In conclusion, appropriate antibiotic therapy and statin use are associated with lower risk of mortality from BSIs in this patient population.

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Introduction

Major advances in transplantation techniques and the understanding of transplant biology have greatly improved the survival of solid-organ transplant recipients. Each year, more than 45,000 people receive intra-abdominal solid-organ transplants, with the 3-year survival of kidney and pancreas recipients being greater than 90% and liver recipients being greater than 75% [1]. Despite these advances, infection in solid-organ transplant recipients remains a challenging problem. Infection now exceeds rejection as the precipitating factor for hospitalization in patients in the first two years after a solid-organ transplant [2]. Bloodstream infections (BSIs) in particular are common in solid-organ transplant recipients [3–5]; however, clinical outcomes of BSIs in solid-organ transplantation have not been adequately characterized.

We performed a retrospective cohort study to determine the microbiology and outcomes of BSIs in the recipients of abdominal solid-organ transplantation.

Methods

Sources of data

ICD-9 codes were used to identify all patients undergoing renal, liver, and kidney–pancreas transplantation at the

University of Wisconsin between 1st January 1995 and 27th November 2006 (n=1,738) who had at least one episode of BSI after transplantation. Data collection included demographics, information pertaining to transplantation, microbiology, treatment-relevant factors, and outcomes, including clinical cure and death within the 15-day period following BSI. Relevant definitions are provided in Table 1. The study protocol was approved by the University of Wisconsin Health Sciences Institutional Review Board.

Immunosuppression

All patients were given peri-operative prophylaxis with cefazolin (renal transplants) and ceftriaxone (liver transplants). Selective digestive decontamination was not used. Induction regimens included one of the following: alemtuzumab (for renal transplants, one 20-mg or two 20-mg doses), basiliximab (two doses of 20 mg on operative day and day 4), daclizumab (1 mg/kg on day of surgery and one dose every other week for a total of five doses), or muromonab-CD3/ATG/Thymoglobulin (SangStat, Fremont, CA) Thymoglobulin was administered at a dose of 1.5 mg/kg daily starting on day 0 (day of transplant) and continued until calcineurin inhibitor levels were therapeutic or a maximum of 14 doses was given. The operating surgeon made the decision to use a particular antibody for induction therapy on the basis of perceived efficacy, side-effect profile, and cost [6]. Thymoglobulin was the generally preferred antibody for re-transplants, although it is not limited to re-transplants. A minimum of four doses of Thymoglobulin was given. Muromonab-CD3 (OKT3; Ortho Biotech, Raritan, NJ) was given at a dose of 5 mg/day for a minimum of seven doses and a maximum of 14 doses. Antithymocyte globulin (ATG; Upjohn, Kalamazoo, MI) was given at a dose of 15 mg/kg intravenously for a minimum of four daily doses and a maximum of 14 doses.

For kidney transplants, maintenance immunosuppression in all groups consisted of either tacrolimus or cyclosporine started when the serum creatinine level declined to less than 3.0 mg/dL. The use of cyclosporine versus tacrolimus was

Table 1 Definitions of variables included in the study

Bloodstream infection (BSI)	Isolation of bacteria other than common skin contaminants from a single blood culture in the presence of signs or symptoms of infection OR isolation of common skin contaminants from two blood cultures in the presence of signs or symptoms of infection
Co-morbidities	
Diabetes	As diagnosed by a clinician
Coronary artery disease (CAD)	As diagnosed by a clinician
Renal disease	Creatinine ≥2 mg/dL
Hemodialysis	Within 30 days prior to BSI
Liver disease	As diagnosed by a clinician, occurring post-transplant and not the primary reason for transplant
Chronic obstructive pulmonary disease (COPD)	As diagnosed by a clinician
Immunosuppression	Any immunosuppressing medication administered prior to BSI
Oral estrogen use	At the time of BSI
Statin use	At the time of BSI
Devices	Any tubes, drains, or vascular lines within 30 days prior to BSI
Surgery	Any surgical procedure within 30 days prior to BSI
Timing of antibiotics	Time in h from positive blood cultures to the initiation of antibiotics
High-grade bacteremia	Positive blood cultures within 12 h of blood draw
Antibiotic resistant	Resistant to ≥2 antibiotics
Appropriate antibiotics	Organism identified was susceptible
Cure of BSI	Resolution of clinical signs or symptoms of infection OR negative blood cultures
Cytomegalovirus infection	Within 30 days prior to BSI
Invasive fungal infection	Blood cultures or tissue samples with fungus within 30 days prior to BSI
Nosocomial infection	BSI occurring >48 h after admission or within 7 days of discharge
Rejection	Pathologic demonstration of transplanted organ rejection within 60 days prior to BSI
Neutropenia	Absolute neutrophil count <500 cells/μl within 30 days prior to BSI
APACHE III score	Calculated based on the 24 h prior to positive blood culture

at the discretion of the transplant surgeons and physicians who cared for these patients. Mycophenolate mofetil (MMF) was used in all patients starting on day 1 at a dose of 1,000 mg twice daily and reduced for symptoms of diarrhea or white blood cell count less than 3.0. In patients who had not received alemtuzumab, steroids were administered at a dose of 500 mg methylprednisolone intravenously on day 0, 250 mg intravenously on day 1, 90 mg orally on day 2, 60 mg on day 3, and 30 mg on day 4 and thereafter. Prednisone was tapered to 10 mg by 3 months in patients without rejection.

For liver transplants, maintenance immunosuppression consisted of tacrolimus with or without a second immunosuppressant, such as MMF, at a dose of 2 to 3 g per day in two divided doses. The tacrolimus doses were adjusted to maintain levels of 5–10 ng/ml.

Prophylaxis

Antifungal prophylaxis included clotrimazole troches or nystatin swish and swallow for 3 months. Fluconazole antifungal prophylaxis is not routinely used at our institution for any of these organ transplant groups. For cytomegalovirus (CMV) prophylaxis in kidney transplant recipients, D+/R– received valganciclovir, D−/R− acyclovir 400 mg twice daily, and D−/R+ received acyclovir 800 mg four times daily if the induction agent was basiliximab. If alemtuzumab or thymoglobulin was used, valganciclovir instead of acyclovir is now used. During the study period, acyclovir was used for CMV prophylaxis in D+/R+ patients. Preemptive therapy or monitoring is not employed at our institution. Liver transplant recipients received valganciclovir for CMV prophylaxis. In the years before valganciclovir became available, oral ganciclovir was used. The duration of CMV prophylaxis was 90 days following transplantation. The treatment of rejection was initiated with high-dose corticosteroids. For steroid refractory rejection, muromonab-CD3 was used.

Statistical analysis

Data on predictors of mortality for patients who died and those who did not were compared using the Chi-square or Fisher's exact test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Full multivariate logistic regression models were used to estimate independent predictors of mortality found to be significant in univariate analysis at $P \leq 0.1$. The Hosmer–Lemeshow test was used to determine the goodness of fit. Analyses were repeated using clinical cure as the outcome. Given the long time frame of this study, an era effect was also included in the analyses. Analyses were conducted using SAS software (version 9.1, 2007; SAS, Cary, NC).

Results

Patient demographics

Overall, 311 patients with 604 episodes of BSI formed the cohort. Fifty-four percent of patients had a single episode of BSI and 25% had two episodes. The remainder had three or more episodes (range 3–10). There were 188 (60%) men and 123 (39%) women. The mean age for the cohort was 51 years (standard deviation [SD] 12.42, range 18–77 years). Most patients had received a kidney transplant (127, 41%), followed by liver (104, 33%), and kidney–pancreas (33, 10%). The remainder of the cohort received simultaneous liver–kidney (11, 3.4%) or other combinations of sequential transplants.

Table 2 Microbiology of the bloodstream infections (BSIs) in the study population

Organism	Frequency (*n*, %)
Gram-positive organisms	149 (45)
Enterococcus	75 (23)
Vancomycin-resistant *Enterococcus*	22 (7)
Coagulase-negative *Staphylococci*	35 (11)
Coagulase-positive *Staphylococci*	23 (7)
Methicillin-resistant *S. aureus*	5 (2)
Streptococcal species	12 (4)
Other[1]	4 (1)
Gram-negative organisms	126 (38)
E. coli	46 (14)
K. pneumoniae	27 (8)
E. cloacae	12 (4)
P. aeruginosa	18 (5)
K. oxytoca	6 (2)
C. freundii	5 (2)
S. marcescens	2 (0.6)
P. mirabilis	2 (0.6)
Other[2]	8 (2)
Anaerobic organisms	6 (2)
Fungi	30 (9)
C. albicans	12 (4)
C. glabrata	13 (4)
Other[3]	5 (2)
Polymicrobial[4]	21 (6)
Total	332

[1] Less than 1% of each of the following: *S. pneumoniae*, *Abiotrophia*, alpha-hemolytic streptococci

[2] Less than 1% of each of the following: *Citrobacter* species, *A. xylosoxidans*, *Acinetobacter* species, *H. influenzae*, *Morganella* species, *Salmonella* species, *Enterobacter* species, *S. maltophilia*

[3] Less than 1% of each of the following: *C. tropicalis*, *A. fumigatus*, *C. parapsilosis*, *C. neoformans*

[4] Two or more organisms in a single blood culture

Table 3 Univariate analysis of clinical cure

	Cured (n=260)	Not cured (n=51)	P-value
Sex, n (%)			
Male	151 (58)	37 (73)	0.05
Female	109 (42)	14 (27)	
Age at time of transplant, mean (SD), years	50.56 (12.61)	53.74 (11.13)	0.09
Transplant type			
Kidney	110 (42)	17 (33)	
Kidney–pancreas	30 (12)	3 (6)	
Liver	81 (31)	23 (45)	
Liver–kidney	8 (3)	3 (6)	0.62
Other	31 (12)	5 (10)	
Immunosuppression			
Prednisone	259 (100)	50 (98)	0.19
Mycophenolate	172 (65)	34 (67)	0.94
Cyclosporine	122 (47)	23 (45)	0.81
Tacrolimus	120 (46)	23 (45)	0.80
Sirolimus	20 (8)	5 (10)	0.89
Azathioprine	71 (27)	10 (20)	0.25
Co-morbidities			
Diabetes	167 (64)	36 (71)	0.63
CAD	117 (45)	27 (53)	0.29
Renal disease	208 (80)	41 (80)	0.94
Hemodialysis	47 (18)	18 (35)	0.005
Liver disease	116 (45)	36 (71)	0.0007
COPD	37 (14)	10 (20)	0.32
Medications			
Estrogen use	15 (6)	1 (2)	0.26
Statin use	70 (27)	8 (16)	0.09
Procedures and devices			
Surgery	100 (38)	27 (53)	0.05
Devices	258 (99)	50 (98)	0.53
ICU care	45 (17)	30 (59)	<0.0001
Antimicrobial use			
Appropriate antibiotic	240 (92)	32 (63)	<0.0001
Clinical signs and symptoms			
Fever	174 (67)	23 (45)	0.003
Hypothermia	16 (6)	11 (22)	0.0004
Hypotension	67 (26)	26 (51)	0.0003
Mental status changes	47 (18)	33 (65)	<0.0001
Neutropenia	21 (8)	11 (22)	0.003
G-CSF	19 (7)	11 (22)	0.001
Need for pressors	19 (7)	20 (39)	<0.0001
High-grade bacteremia	122 (47)	15 (29)	0.02
Nosocomial	124 (48)	38 (75)	0.0005
APACHE III score (mean and SD)	16.28 (5.46)	22.76 (7.86)	<0.0001
MDR pathogen*	93 (36)	26 (51)	0.03
Pre-1995 (pre-tacrolimus and MMF)	71 (27)	16 (31)	0.69
1996–2002 (TAC/CSA-MMF era)	135 (52)	27 (53)	
2003–2006 (alemtuzumab era)	53 (20)	8 (16)	

*MDR = multidrug-resistant (to three or more antimicrobial classes); MMF = mycophenolate mofetil;TAC = tacrolimus; CSA = cyclosporine

Most patients (234, 75%) had a single transplant, 69 (21%) underwent re-transplantation, and ten (3%) had a third transplant.

Ninety-nine percent of patients received prednisone. Forty-eight percent (149) of patients received induction treatment with monoclonal antibody. The monoclonal antibody used was alemtuzumab in 26 patients (26/299, 9%), basiliximab in 53 (53/299, 18%), muromonab in 51 (51/299, 17%), and daclizumab in six (6/299, 2%). For 12 patients, antibody data was not available. ATG was used in 86 patients (86/311, 28%). For the maintenance of immunosuppression, tacrolimus was used in 143 (143/311, 46%) patients, sirolimus in 25 (25/311, 8%), MMF in 206 (206/299, 66%), cyclosporine in 145 (145/311, 46%), and azathioprine in 81 (81/311, 26%).

Overall, 203 patients (65%) had diabetes, 144 (46%) had CAD, 249 (80%) had renal dysfunction, 65 (21%) were receiving hemodialysis, 152 (48%) had liver dysfunction, and 47 (15%) had COPD. Ninety-nine percent of the study population had a device in place.

Estrogen use was recorded in 16 patients (5%). Statins were used by 80 (25%) of the patients.

Signs and symptoms of BSIs

Signs and symptoms were abstracted from data on the chart from 48 h prior to a positive blood culture. One hundred and ninety-seven patients (63%) had fever, 27 (8.6%) were hypothermic, 93 (29%) were hypotensive, 179 (57%) were tachycardic, and 80 (25%) had mental status changes. Thirty-two (10%) were neutropenic and 30 (9%) were receiving granulocyte colony-stimulating factor (G-CSF). Seventy-five (23%) were in the intensive care unit (ICU), 39 (12%) were on pressors, 141 (41%) had high-grade bacteremia (defined as a positive blood culture less than 12 h after drawing the sample), and 162 (55%) were nosocomial BSIs. The mean APACHE score was 17.3 (SD 6.3). The source of bacteremia was pneumonia in 18 (5.9%), abdomen in 97 (31.8), intravascular device in 61 (20%), urinary in 76 (25.5%), and surgical site infection in two (0.6%). In 43 patients, the source could not be determined. Fifty patients had CMV disease. Rejection occurred in 74 patients (24%).

Microbiology

The microbiology of the BSI episodes is shown in Table 2. The majority of BSIs were caused by Gram-positive organisms (45%), followed by Gram-negative organisms (38%) and yeast (9%). Enterococci accounted for 23% of the Gram-positive BSIs. The most frequent Gram-negative organism was *Escherichia coli* (14% of the Gram-negative pathogens). Among the yeast, albicans and non-albicans species were equally distributed. Six percent of the BSIs were polymicrobial.

Treatment of bacteremia

Appropriate antibiotic therapy was defined as therapy to which the infecting organism was susceptible (Table 1). Two hundred and seventy-two patients (87%) received appropriate antibiotic therapy, 121 isolates were pan-susceptible, 71 were resistant to one drug, and 110 were resistant to two or more drugs (multidrug-resistant, MDR). Overall, antibiotics were administered at a mean of 5.92 h (SD 17.28) after a positive blood culture was reported.

Outcomes

Clinical cure was defined as the resolution of clinical signs or symptoms of infection OR negative blood cultures in the two-week period following the BSI. Overall, 260 (84%) were cured, 50 (16%) died during hospitalization, 44 (14%) died within 15 days of BSI, and 93 (31%) died in the first year following BSI. Following BSI, the median length of stay was 14 days (SD 28).

Predictors of clinical cure

Univariate analysis

We compared features of patients with BSI who achieved clinical cure with those who did not to determine predictors of successful treatment. Table 3 shows the features of patients who were cured versus those who were not. Clinical cure was achieved less frequently in women compared with men, in patients on hemodialysis and liver disease, and those who required ICU care. More severely ill patients, such as those with a high APACHE score and on pressors, also achieved clinical cure of bacteremia less frequently. The presence of a multidrug pathogen was found more frequently in patients who did not achieve clinical cure.

Table 4 Independent predictors of achieving clinical cure

Variable	OR (95% CI)	*P*-value
APACHE III score	0.86 (0.79–0.93)	0.0005
Mental status changes	0.28 (0.10–0.80)	0.02
Nosocomial	0.33 (0.12–0.90)	0.03
Lack of appropriate antibiotic therapy	0.06 (0.01–0.18)	<0.0001

The final model contained the following variables: age, gender, APACHE score, comorbidities (dialysis, liver disease), statin use, clinical features (hypothermia, fever, hypotension, mental status changes, ICU care, pressors), multidrug-resistant pathogen, appropriate antibiotic therapy, and origin of bacteremia (nosocomial vs. community)

Table 5 Univariate analysis of 15-day mortality

	Died (n=44)	Survived (n=264)	P-value
Sex, *n* (%)			
Male	31 (70)	157 (60)	0.14
Female	13 (30)	110 (42)	
Age at time of transplant, mean (SD), years	54.06 (12.29)	50.59 (12.39)	0.08
Transplant type			
Kidney	15 (34)	112 (42)	
Kidney–pancreas	4 (9)	29 (11)	0.83
Liver	21 (48)	83 (31)	
Liver–kidney	3 (7)	8 (3)	
Other	1 (2)	35 (13)	
Immunosuppression			
Prednisone	44 (100)	264 (100)	0.56
Mycophenolate	27 (61)	179 (68)	0.46
Cyclosporine	22 (50)	123 (47)	0.62
Tacrolimus	16 (36)	127 (48)	0.16
Sirolimus	4 (9)	21 (8)	0.78
Azathioprine	10 (22)	71 (27)	0.58
Co-morbidities			
Diabetes	30 (68)	173 (66)	0.84
CAD	24 (55)	120 (45)	0.23
Renal disease	35 (80)	214 (81)	0.92
Hemodialysis	14 (32)	51 (19)	0.05
Liver disease	31 (70)	121 (46)	0.002
COPD	11 (25)	36 (14)	0.04
Medications			
Estrogen use	3 (7)	13 (5)	0.58
Statin use	4 (9)	74 (28)	0.008
Procedures and devices			
Surgery	22 (50)	105 (40)	0.18
Devices	43 (98)	264 (100)	0.56
ICU care			
Antimicrobial use			
Appropriate antibiotic	31 (70)	241 (91)	0.0002
Clinical signs and symptoms			
Fever	21 (48)	176 (67)	0.02
Hypothermia	8 (18)	19 (7)	0.01
Hypotension	27 (61)	66 (25)	<0.0001
Mental status changes	31 (70)	49 (19)	<0.0001
Neutropenia	13 (30)	19 (7)	<0.0001
G-CSF	12 (27)	18 (7)	<0.0001
ICU care	28 (64)	47 (18)	<0.0001
Need for pressors	19 (43)	20 (8)	<0.0001
High-grade bacteremia	14 (32)	123 (47)	0.07
Nosocomial	35 (80)	127 (48)	<0.0001
APACHE score (mean and SD)	23.38 (7.77)	16.35 (5.53)	<0.0001
ABx resistance (MDR or not)	21 (48)	98 (37)	0.18
Rejection	7 (16)	67 (25)	0.18
Era effect			
Pre-1995 (pre-tacrolimus and MMF)	15 (34)	70 (27)	0.58
1996–2002 (TAC/CSA-MMF era)	22 (50)	140 (53)	
2003–2006 (alemtuzumab era)	7 (16)	54 (20)	

*MDR = multidrug-resistant; MMF = mycophenolate mofetil; TAC = tacrolimus; CSA = cyclosporine

Multivariate analysis

We constructed logistic regression models to identify independent predictors of clinical cure. The following variables were associated with a reduced likelihood of clinical cure: high APACHE score (each 1 point increase was associated with a 0.86 odds of clinical cure, 95% CI 0.79–0.93), lack of fever (OR 0.33, 95% CI 0.12–0.89), presence of mental status changes (OR 0.28, 95% CI 0.10–0.80), nosocomial rather than community origin of bacteremia (OR 0.33, 95% CI 0.12–0.90, P=0.03), and the lack of appropriate antibiotic therapy (OR 0.06, 95% CI 0.01–0.18) (Table 4).

Predictors of 15-day mortality in patients with BSIs

Univariate analysis

We compared the features of patients with BSIs who died within 15 days with those who did not to determine the predictors of 15-day mortality (Table 5). The mortality rate at 15 days was higher in patients with liver disease and chronic obstructive pulmonary disease. More severely ill patients, such as those in the ICU and on pressors, also had a higher 15-day mortality rate. Nosocomial infection was found more frequently in those who died. In this analysis, statin use was found to be protective.

Multivariate analysis

To determine independent predictors for 15-day mortality following BSI, factors that were clinically and statistically significant in the univariate analysis were entered into logistic regression models. In the final model, each 1 point increase in the APACHE score was associated with a 1.09-fold increased risk of death (OR 1.09, 95% CI 1.00–1.18, P=0.03). Mental status changes was associated with a 3.84-fold increased risk of mortality (OR 3.84, 95% CI 1.36–11.11, P=0.01). The lack of appropriate antibiotic therapy was associated with a four-fold higher risk of death within 15 days of the BSI (4.65, 95% CI 1.46–14.78, P=0.009). Statin use was found to be protective, with an OR of 0.18 (95% CI 0.04–0.78, P=0.04) (Table 6).

Table 6 Independent predictors of 15-day mortality

Variable	OR (95% CI)	P-value
APACHE score	1.09 (1.0–1.18)	0.03
Mental status changes	3.84 (1.36–11.11)	0.01
Statin use	0.18 (0.04–0.78)	0.04
Appropriate antibiotic therapy	4.65 (1.46–14.78)	0.009

The final model contained the following variables: age, gender, APACHE score, comorbidities (dialysis, liver disease), statin use, clinical features (hypothermia, fever, hypotension, mental status changes, ICU care, pressors), multidrug-resistant pathogen, appropriate antibiotic therapy, and origin of bacteremia (nosocomial vs. community)

Discussion

With incidence rates ranging from 7 to 49% [3–7], BSI is a significant problem among recipients of intra-abdominal solid-organ transplants. Previous studies have shown associated mortality rates of 4–11% in kidney recipients and 16–50% in liver recipients [5, 7]. In our series, BSI crude mortality ranged from 13% in kidney to 37% in liver–kidney recipients, reiterating the significance of this problem and the need for further investigation into risk factors and effective strategies for the treatment and prevention of BSIs in this population.

In our study, we found that Gram-positive organisms accounted for the majority of BSIs, followed closely by Gram-negative organisms and yeast. In contrast to other studies that have reported a high incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) BSI in liver transplant patients [7], we found that, in our institution, vancomycin-resistant enterococcus ((VRE) was a more common cause of BSI than MRSA. This is in keeping with the finding that the most common source for BSI was intra-abdominal. Our results are similar to that of a recent study by Torre-Cisneros et al. from Spain that found Gram-positive organisms as the predominant bacteria isolated in cases of early-onset bacteremia, and the most common source, the abdomen (33%) [8]. However, a substantial proportion of the BSIs in our study were related to intravascular devices. Thus, interventions to prevent device-related BSI such as the use of antibiotic or antiseptic locks [9], chlorhexidine sponge dressings [10], chlorhexidine for cutaneous antisepsis [11], and attention to catheter care are particularly relevant in this vulnerable population.

We found that factors independently associated with reduced likelihood of clinical cure included higher APACHE score, lack of fever, altered mental status, nosocomial origin of BSI, and the lack of appropriate antibiotic therapy. Other studies in nontransplant populations have found the lack of appropriate antibiotic therapy to be a major factor impeding clinical and microbiologic cure and increasing mortality [12, 13]. Similar to previously published data showing an inverse relationship between fever and outcome, the lack of fever in our population also portended worse outcomes [7].

We examined risk factors for 15-day mortality in patients with BSIs and found that the mortality risk associated with higher APACHE scores is reflective of earlier studies that

identified sepsis, respiratory failure, and mechanical ventilation as risk factors for mortality [5, 7].

In our study, we did not find a particular pathogen to be associated with increased mortality. Bedini et al. published data from 42 episodes of Gram-positive BSIs in 205 patients over a 6-year period from Italy [6]. Gram-positive BSI was the major independent risk factor for death, reducing survival by 26% in the first year post-transplant. However, the study was limited to Gram-positive bacteremia and a comparative assessment with other organisms causing BSIs was not possible.

Antibiotic resistance has been linked with poor outcomes in BSIs in some studies [14–16]. In their study of solid-organ and hematologic transplant recipients in Spain, Moreno et al. found that multidrug-resistant Gram-negative BSIs had worse prognosis than infection caused by susceptible Gram-negative bacteria [5]. However, the predictors of outcome and treatment-related factors were not examined [5]. Gearhart et al. found that liver transplant patients with VRE had a lower survival compared with controls without VRE infection (52% vs. 82%; P=0.048) and an increased cost of care [17]. We found that multidrug resistance was associated with a poor outcome in terms of clinical cure in the univariate analysis, but this variable did not reach statistical significance in the multivariate analyses. In our study, however, the proportion of multidrug-resistant organisms in our sample was small.

To our knowledge, the role of statins in modifying outcomes of BSIs has not previously been examined in transplant recipients. Our analysis showed that the use of statins within 30 days prior to BSI was associated with a reduction in 15-day mortality. An emerging body of literature suggests that statins may improve outcomes in nontransplant patients with bacteremia, sepsis, and multi-organ dysfunction [18–22]. Observational studies have also shown that patients receiving statins are less likely to develop severe sepsis [23, 24]. Gupta et al. showed that statins were strongly and independently associated with the reduction of the risk of hospitalization in patients with chronic kidney disease and on hemodialysis [24]. Possible mechanisms for the protection afforded by statins include immunomodulatory and anti-inflammatory properties by the modification of cellular chemotaxis and intercellular interactions. Additionally, statins lower cytokine release, lower acute phase reactant proteins, and act as anti-oxidants, all of which may provide protective effects in BSIs and sepsis [25]. Given the high mortality of BSIs in the transplant population, the role of statins deserves further attention. While a large randomized trial of statins in renal transplantation (ALERT) for lipid-lowering and cardiovascular outcomes failed to show a mortality advantage overall [26], it remains possible and biologically plausible that statins may yield benefits in mitigating adverse outcomes from sepsis, and further research is needed.

The current study has a number of limitations, most importantly the retrospective design, with its inherent limitations that precluded us from examining in further detail the role of statins in the outcomes of BSIs, such as dosage and the duration of statin use. Bias in the ascertainment of exposure is a concern in a case–control study. We mitigated against this by using a standard data extraction form and using identical sources of data extraction for all subjects in the study. We examined mortality after BSI, but not graft survival, which may be an important secondary outcome.

In conclusion, we found that, in recipients of intra-abdominal transplants, BSI is associated with high mortality and statins are associated with improved outcomes. Future prospective studies are needed to further examine the relationship between statins and improved survival in transplant patients.

Conflicts of Interest No conflicts of interest for all authors

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