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Bacteremia in solid organ transplant recipients as compared to immunocompetent patients: Acute phase cytokines and outcomes in a prospective, matched cohort study

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Abstract

We undertook a prospective, matched cohort study of patients with *Staphylococcus aureus* bacteremia (SAB) and gram-negative bacteremia (GNB) to compare the characteristics, outcomes, and chemokine and cytokine response in transplant recipients to immunocompetent, nontransplant recipients. Fifty-five transplant recipients (GNB $n = 29$; SAB $n = 26$) and 225 nontransplant recipients (GNB $n = 114$; SAB $n = 111$) were included for clinical analysis. Transplant GNB had a significantly lower incidence of septic shock than nontransplant GNB (10.3% vs 30.7%, $p = .03$). Thirty-day mortality did not differ significantly between transplant and nontransplant recipients with GNB (10.3% vs 15.8%, $p = .57$) or SAB (0.0% vs 11.7%, $p = .13$). Next, transplant patients were matched 1:1 with nontransplant patients for the chemokine and cytokine analysis. Five cytokines and chemokines were significantly lower in transplant GNB vs nontransplant GNB: IL-2 (median [IQR]: 7.1 pg/ml [7.1, 7.1] vs 32.6 pg/ml [7.1, 88.0]; $p = .001$), MIP-1β (30.7 pg/ml [30.7, 30.7] vs 243.3 pg/ml [30.7, 344.4]; $p = .001$), IL-8 (32.0 pg/ml [5.6, 53.1] vs 59.1 pg/ml [39.2, 119.4]; $p = .003$), IL-15 (12.0 pg/ml [12.0, 12.0] vs 12.0 pg/ml [12.0, 126.7]; $p = .03$), and IFN-α (5.1 pg/mL [5.1, 5.1] vs 5.1 pg/ml [5.1, 26.3]; $p = .04$). Regulated upon Activation, Normal T Cell Expressed and Secreted (RANTES) was higher in transplant SAB vs nontransplant SAB (mean [SD]: 750.2 pg/ml [194.6] vs 656.5 pg/ml [147.6]; $p = .046$).

KEYWORDS
clinical research/practice, cytokines/cytokine receptors, immunosuppression/immune modulation, infection and infectious agents – bacterial, infectious disease, organ transplantation in general, translational research/science

Abbreviations: AKI, acute kidney injury; APS, acute physiology score; BSIB, bloodstream infection biorepository; CMV, cytomegalovirus; GI, gastrointestinal; GM-CSF, granulocyte-macrophage colony-stimulating factor 2; GNB, gram-negative bacteremia; GU, genitourinary; HIV, human immunodeficiency virus; IFN-γ, interferon gamma; IFN-α, interferon alpha; IL-10, interleukin 10; IL-12, interleukin 12; IL-13, interleukin 13; IL-15, interleukin 15; IL-17A, interleukin 17A; IL-1RA, interleukin 1 receptor antagonist; IL-1β, interleukin 1 beta; IL-2, interleukin 2; IL-2R, interleukin 2 receptor; IL-4, interleukin 4; IL-5, interleukin 5; IL-6, interleukin 6; IL-7, interleukin 7; IL-8, interleukin 8; IP-10, interferon-inducible protein 10; IQR, interquartile range; KDIGO, kidney disease: improving global outcomes; MCP-1, monocyte chemoattractant protein 1; MDR, multidrug resistant; MIC, minimum inhibitory concentration; MIG, monokine induced by gamma interferon; MIP-1β, macrophage inflammatory protein 1 beta; MIP-1α, macrophage inflammatory protein 1 alpha; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; SAB, *Staphylococcus aureus* bacteremia; SD, standard deviation; TNF-α, tumor necrosis factor alpha.

1 | INTRODUCTION

Solid organ transplantation has revolutionized the prognosis of patients with end-stage organ disease. Long-term immunosuppression is fundamental to graft survival, yet confers an increased risk of infection.[1] Although bacteremia is a leading cause of death in patients who have undergone solid organ transplantation,[2] the epidemiology and risk factors for adverse outcomes of bacteremia in this population are incompletely understood. The potential impact of long-term therapeutic immunosuppression on host inflammatory response to bacteremia among transplant recipients is also poorly understood. Prior investigators have suggested that immunosuppression in patients with bacteremia should be temporarily reduced out of concern for increased risk for morbidity and mortality from sepsis,[2,3] though this remains an area in need of research.

The host immune response to bacteremia involves a cascade of pro-and anti-inflammatory cytokines and chemokines. Specific cytokines are associated with gram-negative vs gram-positive bacterial infections, as well as with adverse outcomes.[4-8] However, no study to date has reported cytokine or chemokine levels in solid organ transplant recipients with bacteremia or compared them to cytokine levels seen in bacteremic patients without organ transplantation. In the current investigation, we used a prospective, matched cohort design to define the epidemiology, outcomes, and host inflammatory response to *Staphylococcus aureus* bacteremia (SAB) and gram-negative bacteremia (GNB) in patients with and without solid organ transplantation.

2 | METHODS

2.1 | Study design and sample

All eligible inpatients with either monomicrobial SAB or GNB from February 8, 2006 to April 27, 2015 at Duke University Medical Center and Duke Regional Hospital were prospectively enrolled in the Bloodstream Infections Biorepository (BSIB). Clinical data, microbiologic specimens, and patient sera were secured for all enrolled patients. Patients from the BSIB were eligible for inclusion into the present study if they were bacteremic with *S. aureus*, *Escherichia coli*, or *Klebsiella pneumoniae*. The GNB population was restricted to patients with bacteremia due to *E. coli* and *K. pneumoniae* to minimize inflammatory response heterogeneity potentially introduced by multiple bloodstream pathogens. From this cohort, patients who were recipients of a solid organ transplant (lung, heart, kidney, liver, pancreas, or combination therein) were included for analysis. The control group was composed all immunocompetent nontransplanted patients who were bacteremic with the same organism and had requisite sera available for cytokine and chemokine analysis. Patients not meeting the definition of "immunocompetent" (defined below) were excluded.

For the chemokine and cytokine analysis, transplant BSIB patients were matched 1:1 with nontransplant BSIB patients. Subjects were matched on age, race, gender, bacteria species, and methicillin resistance status (if SAB). Matching was performed by an investigator (F.R.) who was blinded to clinical outcome. In the event where there was more than one potential matched control for a given transplant subject, the matched control was selected at random.

This study was IRB approved. Patients (or their legally authorized representative) provided written informed consent. If a patient died prior to notification of blood culture results, the subjects were enrolled using an IRB-approved Notification of Decedent Research.

2.2 | Definitions

Immunocompetent was defined as an absence of any of the following comorbidities: (a) diabetes mellitus, (b) human immunodeficiency virus (HIV), (c) hemodialysis dependence, (d) active malignancy, and (e) receipt of immunosuppressive medication (i.e., corticosteroids greater than the equivalent of 10 mg prednisone daily, antiproliferative agents, biologics, monoclonal antibodies, calcineurin inhibitors, or mTOR inhibitors). *Route of infection* was classified as (a) hospital-acquired, (b) community-acquired, health care-associated, or (c) community-acquired, non-health care-associated, in accordance with prior definitions.[9] *Source of infection* was defined as the primary focus of the bacteremia using the standardized CDC/NHSN criteria[10] and was adjudicated independently by two independent reviewers (E.E. and M.D.) with differences resolved by consensus. Bacteremia with no single identifiable source was placed in the "unknown" category. Persistent GNB was defined as positive follow-up blood culture with the same organism drawn at least 24 h after initial culture.[11] Persistent SAB was defined as positive follow-up blood culture with the same organism drawn ≥5 days after initial culture.[12] Patients were considered to have metastatic infection if they developed any of the following: infective endocarditis, septic emboli, septic thrombophlebitis, vertebral osteomyelitis, septic arthritis, a metastatic abscess, or other deep tissue abscess, as defined in Souli et al.[12] *Duration of symptoms* was defined as the patient-reported time from the onset of symptoms to the date of first positive blood culture. *Need for invasive procedure* was defined as requiring a surgical intervention to control or treat the infection (i.e., joint washout, incision and drainage of an abscess, cardiac device removal, chest tube placement, or percutaneous nephrostomy tube placement). APACHE-II scores, including *Acute Physiology Scores* (APS), were calculated on the day of index positive blood culture.[13] All-cause mortality was reported at 30 and 90 days from the date of first positive blood culture.

Acute kidney injury (AKI) was defined as serum creatinine reaching 1.5 times the baseline or increase by ≥0.3 mg/dl within 48 h of onset of bacteremia in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[14] *Septic shock* was defined as sepsis with hypotension (systolic blood pressure ≤90 mm Hg) and

perfusion abnormalities as previously described.[15] Transplant recipients were defined as having a *reduction in immunosuppression* if the patient's immunosuppressive medication was removed, dose-reduced (if an antimetabolite) or goal calcineurin inhibitor trough was reduced at any time during the hospitalization after the diagnosis of bacteremia was made.

2.3 | Laboratory studies

Bacterial isolates were speciated by the Duke Clinical Microbiology Laboratory using standard techniques. Minimum inhibitory concentration (MIC) values were determined using the MicroScan Walkaway system (microbroth dilution method) as described previously. The MIC breakpoint values for each antibiotic were defined according to the most recent Clinical and Laboratory Standards Institute guidelines.[16] Multidrug-resistant (MDR) phenotype was defined as nonsusceptible to at least one antibiotic in ≥3 relevant antimicrobial categories.[17]

2.4 | Cytokine and chemokine profiling

Acute phase serum samples were collected within 72 h of index positive blood culture. Serum cytokines and chemokines were quantified using a 25-plex bead array assay (Invitrogen LHC0009M) performed according to the manufacturer's recommended protocol and read using a Bio-Plex 200 reader (Bio-Rad). The included cytokines and chemokines were eotaxin, granulocyte-macrophage colony-stimulating factor 2 (GM-CSF), interferon alpha (IFN-α), interferon gamma (IFN-γ), interleukin 1 beta (IL-1β), interleukin 1 receptor antagonist (IL-1RA), interleukin 10 (IL-10), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 15 (IL-15), interleukin 17A (IL-17A), interleukin 2 (IL-2), interleukin 2 receptor (IL-2R), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 8 (IL-8), interferon-inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), monokine induced by gamma interferon (MIG), macrophage inflammatory protein 1 alpha (MIP-1α), macrophage inflammatory protein 1 beta (MIP-1 β), RANTES, and tumor necrosis factor alpha (TNF-α). Data were analyzed using Bio-Plex Manager software (Bio-Rad). Any analyte concentration below the lower limit of quantitation was replaced with one-half of the lower limit of quantitation.

2.5 | Statistical methods

Results were summarized using mean with standard deviation (SD), median with interquartile range (IQR), or with frequency with percentage where appropriate. Reviewer agreement for source of infection was assessed by using the Cohen's kappa test. To determine the effect of transplantation status on clinical characteristics and outcomes for GNB and SAB, respectively, Wilcoxon rank sum test was used to analyze continuous variables and chi-squared or Fisher's exact test was used for categorical variables. Chi-squared or Fisher's exact test was used to assess whether there was a relationship between the type of bacteremia and the induction therapy, and between immunosuppressive medication and related outcomes in the transplanted sample. The effect of transplantation status on each of the 25 cytokines and chemokines for GNB and SAB, respectively, was assessed using either the equal or unequal variance version of the Student's *t* test or Wilcoxon rank sum test. For cytokines and chemokines that demonstrated a statistically significant relationship with transplantation status, multiple gamma regression models with a log link were assessed to determine the effect of transplantation status after accounting for the source of infection, immunosuppressive regimen, duration of symptoms, and septic shock. To assess the relationship between transplantation status and 30-day mortality, a logistic regression model was postulated for GNB and SAB, respectively, after adjusting for duration of symptoms and source of infection. The threshold for assessing statistical significance was set at two-sided alpha = 0.05. Analyses were conducted using SAS 9.4 Statistical Software (SAS Institute Inc.).

3 | RESULTS

3.1 | Clinical characteristics of the study sample

A total of 2633 patients were enrolled in the BSIB during the study period. After applying the inclusion and exclusion criteria, 280 patients (10.6%) with bacteremia were identified for analysis (Figure 1). Fifty-five of the patients were transplant recipients (GNB $N = 29$ and SAB $N = 26$).

The demographic and clinical characteristics are reported in Table 1. Overall, route of infection differed significantly between transplant and nontransplant GNB ($p < .0001$) and transplant and nontransplant SAB ($p = .003$). None of the transplant recipients developed community-acquired, non-health care-associated bacteremia (GNB: 0% transplant vs. 37.7%, SAB: 0% transplant vs. 27.0% nontransplant). Among the GNB patients, GU source was the most common source in the transplant and nontransplant groups (51.7% and 45.6%, respectively), followed by GI (20.7% and 28.9%, respectively). Among SAB patients, source of infection significantly differed between transplant and nontransplant groups ($p = .0005$). An endovascular source of SAB was more common in the transplant group as compared to the nontransplant group (transplant: 53.8% and nontransplant: 16.2%), whereas a skin/soft tissue source was the leading identifiable source of infection in the nontransplant group (transplant: 7.7% and nontransplant: 24.3%). Between the two independent reviewers, agreement for the source of infection was high for GNB ($\kappa = 0.99$, $p < .0001$) and for SAB ($\kappa = 0.95$, $p < .0001$). Duration of symptoms was significantly shorter for transplant SAB compared to nontransplant SAB (median [IQR] 1.0 days [1.0, 2.0] vs 4.0 [1.0, 7.0], $p = .0002$). The APACHE II score was significantly higher in the bacteremic

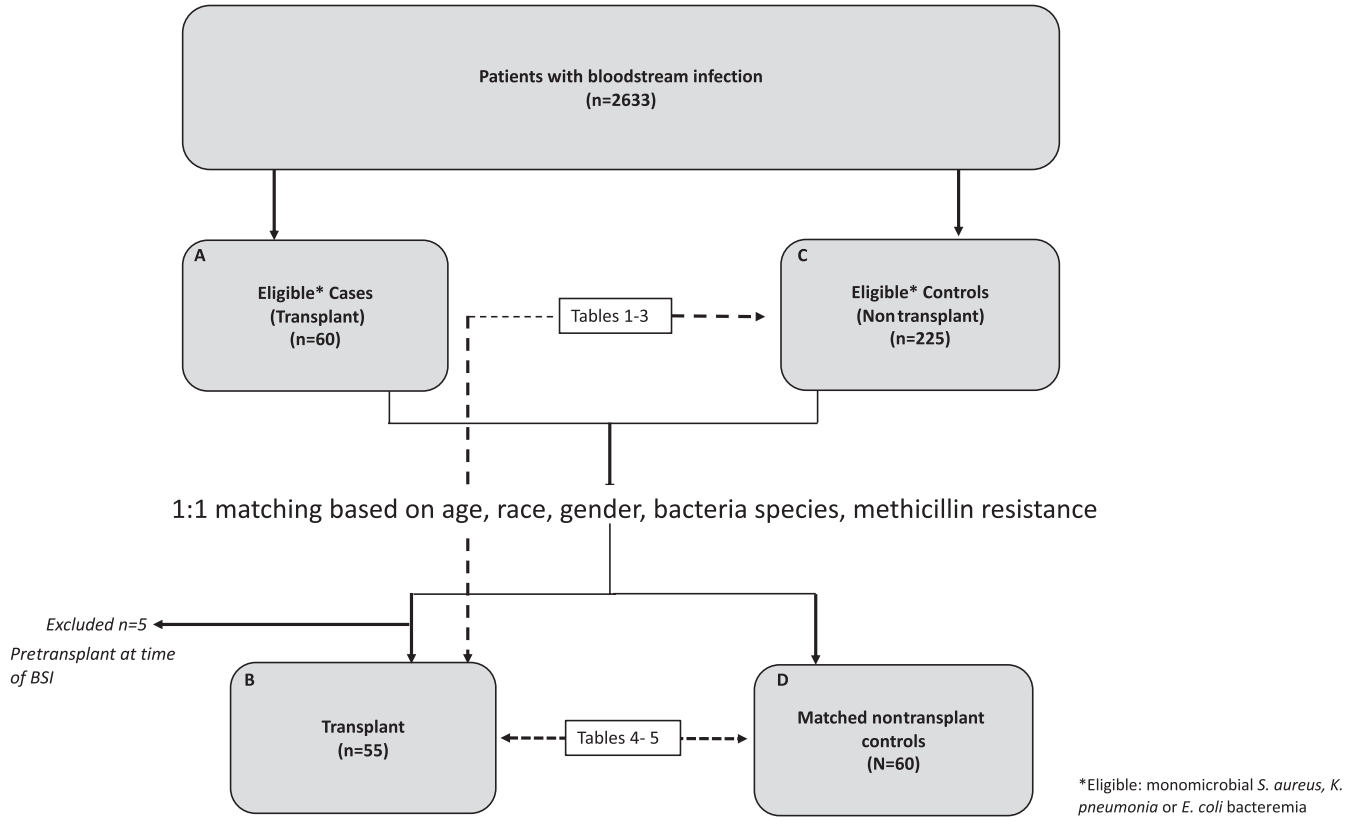

FIGURE 1 Study design. Clinical analysis was performed on the 55 transplant cases and 227 eligible controls (Boxes B and C). Corresponding tables for this comparison are Tables 1–3. Chemokine and cytokine analysis was performed on the 55 transplant cases and 60 matched controls (Boxes B and D). Corresponding tables for this comparison are Tables 4 and 5. SAB, *S. aureus* bacteremia; GNB, gram-negative bacteremia

transplant compared to nontransplant groups: (median [IQR]: transplant GNB 15.0 [13.0, 16.0] vs nontransplant GNB 12.0 [9.0, 16.0], p = .02; transplant SAB 15.5 [13.0, 20.0] vs nontransplant SAB 12.0 [9.0, 16.0], p = .004). The Acute Physiology Score was significantly higher in the transplant SAB group compared to non-transplant SAB group (median [IQR]: 8.0 [5.0, 12.0] vs 5.0 [2.0, 9.0]; p = .01).

3.2 | Clinical outcomes of the study sample

Clinical outcomes are reported in Table 2. For GNB, the rate of septic shock was lower in the transplant group compared to the nontransplant group (10.3% vs 30.7%, p = .03). Hemodialysis-dependent patients were excluded from the nontransplant population, but were eligible for inclusion in the transplant population. Hence, among non-hemodialysis–dependent patients, the rate of AKI in patients with SAB was significantly higher among transplant recipients than nontransplant recipients (transplant SAB 73.3% vs nontransplant SAB 31.5%, p = .002). The incidence of AKI among bacteremic patients did not significantly differ by the type of organ transplanted (Table S1). There were no observed differences in mortality at 30 or 90 days between transplant and nontransplant recipients with either GNB or SAB, respectively. After adjusting for duration of symptoms and source of infection, we did not find evidence of a significant relationship between transplant status and 30-day mortality among patients with GNB (Table 3). A similar model could not be evaluated for SAB because all 13 of the SAB patients who died within 30 days were nontransplant recipients. All patients were rapidly initiated on adequate empiric antimicrobial therapy due to the institutional practice of commencing vancomycin and a broad-spectrum beta-lactam at the time of suspected bloodstream infection. Additionally, all infected or suspected infected central intravenous catheters were removed in accordance with standard institutional practice. Twelve (41.3%) transplant recipients with GNB and eight (30.8%) with SAB underwent reduction of immunosuppression after the diagnosis of bloodstream infection.

3.3 | Inflammatory cytokine and chemokine levels in acute phase sera

Next, we compared the levels of inflammatory cytokines in the acute phase sera of patients with and without organ transplantation who were bacteremic with the same pathogen (e.g., *S. aureus* or GNB) (Table 4). Among patients with GNB, transplant recipients exhibited significantly lower levels of IL-2 (median [IQR]: 7.1 pg/ml [7.1, 7.1] vs 32.6 pg/ml [7.1, 88.0]; p = .001), MIP-1β (30.7 pg/ml [30.7, 30.7] vs

TABLE 1 Clinical characteristics of transplant and nontransplant recipients with bacteremia

Characteristic	No. (%) of patients					
	Transplant GNB *N* = 29	Nontransplant GNB *N* = 114	*p* value	Transplant SAB *N* = 26	Nontransplant SAB *N* = 111	*p* value
Age, median (IQR)	58.0 (42.0, 67.0)	61.5 (50.0, 77.0)	.10[a]	55.0 (45.0, 62.0)	60.0 (46.0, 70.0)	.16[a]
Gender (female)	12 (41.4%)	54 (47.4%)	.56[b]	10 (38.5%)	48 (43.2%)	.66[b]
Race (black)	8 (27.6%)	30 (26.3%)	.89[b]	11 (42.3%)	24 (21.6%)	.03[b]
Organ transplanted						
Lung	5 (17.2%)	–		9 (34.6%)	–	
Heart	3 (10.3%)	–		4 (15.4%)	–	
Kidney	15 (51.7%)	–		11 (42.3%)	–	
Liver	3 (10.3%)	–		2 (7.7%)	–	
Lung and kidney	1 (3.4%)	–			–	
Kidney and pancreas	1 (3.4%)	–			–	
Liver and kidney	1 (3.4%)	–			–	
Months from transplant to bacteremia, median (IQR)	62.9 (9.2, 226.3)	–	–	125.9 (17.5, 271.6)	–	–
Route						
Hospital-acquired	5 (17.2%)	21 (18.4%)	<.0001[c]	7 (26.9%)	21 (18.9%)	.003[c]
Community-acquired, health care-associated	24 (82.8%)	50 (43.9%)		19 (73.1%)	60 (54.1%)	
Community-acquired, non-health care-associated	0 (0.0%)	43 (37.7%)		0 (0.0%)	30 (27.0%)	
Source						
Unknown	2 (6.9%)	11 (9.6%)	.81[c]	2 (7.7%)	32 (28.1%)	.0005[c]
Bone	0 (0.0%)	1 (0.9%)		0 (0.0%)	6 (5.4%)	
Endovascular infection	2 (6.9%)	6 (5.3%)		14 (53.8%)	18 (16.2%)	
CNS	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (0.9%)	
GI infection	6 (20.7%)	33 (28.9%)		1 (3.8%)	3 (2.7%)	
GU infection	15 (51.7%)	52 (45.6%)		0 (0.0%)	2 (1.8%)	
Respiratory/lung	3 (10.3%)	6 (5.3%)		7 (26.9%)	13 (11.7%)	
Skin/soft tissue	1 (3.4%)	2 (1.8%)		2 (7.7%)	27 (24.3%)	
Joint	0 (0.0%)	3 (2.6%)		0 (0.0%)	10 (9.0%)	
Duration of symptoms (days)	2.0 (1.0, 5.0)	1.0 (1.0, 4.0)	.33[a]	1.0 (1.0, 2.0)	4.0 (1.0, 7.0)	.0002[a]
APACHE II, median (IQR)	15.0 (13.0, 16.0)	12.0 (9.0, 16.0)	.02[a]	15.5 (13.0, 20.0)	12.0 (9.0, 16.0)	.004[a]
APS, median (IQR)	7.0 (4.0, 9.0)	6.0 (3.0, 10.0)	.93[a]	8.0 (5.0, 12.0)	5.0 (2.0, 9.0)	.01[a]
MDR organism	4 (13.8%)	16 (14.0%)	1.00[c]			

Abbreviations: GNB, gram-negative bacteremia; SAB, *S. aureus* bacteremia; IQR, interquartile range; SD, standard deviation; CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; APS, acute physiology score; MDR, multidrug resistant.

[a]Wilcoxon.

[b]Chi-square.

[c]Fisher exact.

243.3 pg/ml [30.7, 344.4]; p = .001, IL-8 (32.0 pg/ml [5.6, 53.1] vs 59.1 pg/ml [39.2, 119.4]; p = .003), IL-15 (12.0 pg/ml [12.0, 12.0] vs 12.0 pg/ml [12.0, 126.7]; p = .03), and IFN-α (5.1 pg/ml [5.1, 5.1] vs 5.1 pg/ml [5.1, 26.3]; p = .04) (Figure 2). Among patients with SAB, transplant recipients exhibited significantly higher levels of RANTES (mean [SD]: 750.2 pg/ml [194.6] vs 656.5 pg/ml [147.6]; p = .046). After adjusting for source of infection, immunosuppression class, duration of symptoms and septic shock, IL-2 in GNB was the only cytokine where the statistically significant relationship between transplantation status and cytokine concentration remained significant (Table 5).

Cytokine concentrations were also compared between transplant recipients who did and did not undergo reduction of immunosuppression (Table S2). Among transplant recipients with GNB, patients with immunosuppression reduction had significantly higher levels of MIG (median [IQR]: 185.0 pg/ml [86.5, 319.4] vs 71.8 [63.8,

TABLE 2 Outcomes of transplant and nontransplant recipients with bacteremia

Characteristic	No. (%) of patients					
	Transplant GNB *N* = 29	Nontransplant GNB *N* = 114	*p* value	Transplant SAB *N* = 26	Nontransplant SAB *N* = 111	*p* value
Septic shock	3 (10.3%)	35 (30.7%)	.03[c]	3 (11.5%)	14 (12.6%)	.88[c]
Disseminated intravascular coagulation	0 (0.0%)	3 (2.6%)	1.00[d]	1 (3.8%)	0 (0.0%)	.19[d]
Acute lung injury/acute respiratory distress	1 (3.4%)	10 (8.8%)	.46[d]	1 (3.8%)	9 (8.1%)	.69[d]
Acute Kidney Injury	16 (64.0%)	58 (50.9%)	.23[c]	11 (73.3%)	35 (31.5%)	.002[c]
Metastatic infection	–	–	–	10 (38.5%)	60 (54.1%)	.19[d]
Infective endocarditis	–	–	–	5 (19.2%)	17 (15.3%)	.57[d]
Persistent bacteremia	3 (10.3%)	10 (8.8%)	.73[d]	6 (23.1%)	47 (42.3%)	.08[d]
Clostridium difficile colitis within 1-year postbacteremia	1 (3.4%)	10 (8.8%)	.46[d]	4 (15.4%)	6 (5.4%)	.10[d]
Reduction in Immunosuppression	12 (41.4%)	–		8 (30.8%)	–	
Length of stay (days), median (IQR)	9.0 (6.0, 12.0)	7.0 (4.0, 13.0)	.12[e]	10.5 (7.0, 25.0)	14.0 (8.0, 25.0)	.47[e]
30-day all-cause mortality	3 (10.3%)	18 (15.8%)	.57[d]	0 (0.0%)	13 (11.7%)	.13[d]
90-day all-cause mortality	3 (10.3%)	24 (21.1%)	.29[d]	3 (11.5%)	21 (18.9%)	.57[d]

Abbreviations: GNB, gram-negative bacteremia; SAB, *S. aureus* bacteremia; IQR, interquartile range.

[a]11 of the 16 transplant GNB were kidney transplant recipients.

[b]3 of the 11 transplant SAB were kidney transplant recipients.

[c]Chi-square.

[d]Fisher exact.

[e]Wilcoxon.

88.0]; $p = .04$). Among transplant patients with SAB, patients with immunosuppression reduction had significantly lower levels of Eotaxin (mean [SD]: 47.4 [18.8] vs. 86.8 [64.5]; $p = .04$). There were no differences in the levels of measured cytokines or chemokines between patients with bacteremia due to *K. pneumoniae* vs. *E. coli* (data not shown).

4 | DISCUSSION

Our study challenges the long-held assumption that the pharmacologic immunosuppression of transplant recipients contributes to a worse overall outcome in the setting of bacteremia. In a carefully matched prospective cohort study design that addressed multiple clinical confounders, we found that patients with and without organ transplantation who developed bacteremia did not experience significant differences in the rate of mortality, and that transplant recipients with GNB experienced a significantly lower incidence of septic shock than nontransplant recipients.

We found no significant difference in mortality between bacteremic patients with and without solid organ transplantation for the GNB and SAB groups, respectively. Specifically, after adjusting for relevant confounders, we did not find evidence of a significant change in odds of 30-day mortality based on transplant status. While our sample was underpowered to detect such differences in mortality, our results generally agree with two recent studies of bacteremia in solid organ transplant recipients which found lower rates of 30-day mortality among transplant recipients as compared to nontransplant recipients.[18,19] There are two possible explanations for these results. First, it is possible that

TABLE 3 Odds ratios and 95% confidence intervals for the relationship between transplantation status and 30-day mortality in GNB after adjusting for relevant confounders

Logistic regression model showing the relationship between transplantation status and 30-day mortality after adjusting for relevant confounders for GNB (*N* = 141)		
Variable	**OR (95% CI)**	***p*-value**
Transplantation status (reference = no transplant)	0.61 (0.16, 2.32)	.47
Duration of symptoms (reference = less than 2 days)	0.65 (0.24, 1.75)	.39
Source of infection (reference = unknown)		
Source of infection: GI	0.28 (0.05, 1.64)	.16
Source of infection: GU	0.47 (0.10, 2.09)	.32
Source of infection: other	1.311 (0.26, 6.60)	.74

Abbreviations: GNB, gram-negative bacteremia, CI, confidence interval; GI, gastrointestinal; GU, genitourinary.

TABLE 4 Cytokine concentration by transplant status

Cytokine concentration (by transplant status)						
	Transplant GNB (*N* = 29)	Nontransplant GNB (*N* = 30)	*p* value	Transplant SAB (*N* = 26)	Nontransplant GNB (*N* = 30)	*p* value
Eotaxin, median (IQR)	34.9 (23.4, 39.9)	37.8 (24.5, 44.0)	.51[a]	52.7 (32.5, 87.4)	54.9 (39.9, 89.4)	.85[a]
IFN-α, median (IQR)	5.1 (5.1, 5.1)	5.1 (5.1, 26.3)	.04[a]	5.1 (5.1, 36.4)	5.1 (5.1, 24.0)	.38[a]
IL-1RA, median (IQR)	331.3 (194.4, 699.8)	566.1 (365.4, 1826.0)	.06[a]	842.2 (411.9, 1712.8)	748.7 (509.9, 1942.2)	.79[a]
IL-10, median (IQR)	6.0 (6.0, 6.0)	6.0 (6.0, 6.0)	.67[a]	6.0 (6.0, 34.2)	6.0 (6.0, 33.3)	.80[a]
IL-12, median (IQR)	81.6 (47.3, 134.4)	68.6 (34.3, 103.2)	.40[a]	84.8 (40.6, 235.6)	138.3 (75.0, 333.0)	.19[a]
IL-15, median (IQR)	12.0 (12.0, 12.0)	12.0 (12.0, 126.7)	.03[a]	11.3 (11.3, 92.4)	11.3 (11.3, 92.4)	.91[a]
IL-2, median (IQR)	7.1 (7.1, 7.1)	32.6 (7.1, 88.0)	.001[a]	6.9 (6.9, 95.9)	28.6 (6.9, 98.8)	.86[a]
IL-2R, median (IQR)	74.6 (28.5, 189.1)	134.3 (28.5, 298.4)	.46[a]	266.9 (120.8, 467.4)	221.1 (28.4, 330.6)	.48[a]
IL-6, median (IQR)	25.9 (3.5, 86.5)	38.7 (15.8, 97.2)	.21[a]	56.2 (15.6, 97.7)	72.7 (34.0, 102.3)	.28[a]
IL-8, median (IQR)	32.0 (5.6, 53.1)	59.1 (39.2, 119.4)	.003[a]	84.4 (38.7, 114.8)	103.0 (62.5, 254.4)	.09[a]
IP-10, median (IQR)	6.8 (4.2, 12.7)	6.2 (3.8, 11.9)	.74[a]	6.9 (4.3, 16.2)	10.1 (3.9, 17.1)	.80[a]
MCP-1, median (IQR)	496.5 (291.1, 728.4)	448.6 (355.8, 807.7)	.84[a]	736.5 (412.7, 1142.8)	912.7 (469.2, 1458.9)	.51[a]
MIG, median (IQR)	82.7 (65.2, 226.0)	75.9 (13.1, 139.1)	.43[a]	204.6 (72.0, 357.1)	149.1 (94.0, 211.7)	.36[a]
MIP-1α, median (IQR)	8.9 (8.9, 8.9)	8.9 (8.9, 8.9)	.21[a]	8.8 (8.8, 49.1)	8.8 (8.8, 44.8)	.86[a]
MIP-1β, median (IQR)	30.7 (30.7, 30.7)	243.3 (30.7, 344.4)	.001[a]	193.6 (88.0, 362.7)	234.3 (131.0, 444.8)	.29[a]
RANTES, mean (SD)	544.8 (106.5)	523.4 (137.3)	.51[b]	750.2 (194.6)	656.5 (147.6)	.046[b]
GM-CSF, median (IQR)	3.5 (3.5, 3.5)	3.5 (3.5, 3.5)	.62[a]	3.5 (3.5, 3.5)	3.5 (3.5, 3.5)	.32[a]
IFN-γ, median (IQR)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)	.34[a]	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)	.38[a]
IL-1β, median (IQR)	6.1 (6.1, 6.1)	6.1 (6.1, 6.1)	.33[a]	6.0 (6.0, 6.0)	6.0 (6.0, 6.0)	.29[a]
IL-13, median (IQR)	7.2 (7.2, 7.2)	7.2 (7.2, 7.2)	.[b]	6.9 (6.9, 6.9)	6.9 (6.9, 6.9)	.92[a]
IL-17A, median (IQR)	14.9 (14.9, 14.9)	14.9 (14.9, 14.9)	.[b]	14.9 (14.9, 14.9)	14.9 (14.9, 14.9)	.30[a]
IL-4, median (IQR)	31.4 (31.4, 31.4)	31.4 (31.4, 31.4)	.33[a]	30.6 (30.6, 30.6)	30.6 (30.6, 30.6)	.73[a]
IL-5, median (IQR)	5.1 (5.1, 5.1)	5.1 (5.1, 5.1)	.[b]	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	.[b]
IL-7, median (IQR)	9.4 (9.4, 9.4)	9.4 (9.4, 9.4)	.32[a]	9.0 (9.0, 9.0)	9.0 (9.0, 9.0)	.29[a]
TNF-α, median (IQR)	2.9 (2.9, 2.9)	2.9 (2.9, 2.9)	.33[a]	2.8 (2.8, 2.8)	2.8 (2.8, 2.8)	.92[a]

Abbreviations: GNB, gram-negative bacteremia; SAB, *S. aureus* bacteremia.

[a]Wilcoxon.

[b]Equal variance *T* test.

transplant recipients who develop bacteremia experience shorter time to symptom recognition, medical evaluation, and empiric antibiotic therapy due to close contact with their transplant team and the health-care system. Indeed, the transplant recipients with SAB had a significantly shorter duration of symptoms compared to nontransplant recipients. Second, it is possible that the immunosuppressants taken by transplant recipients may attenuate the paradoxically deleterious effects of exuberant inflammatory responses that can occur during sepsis, a concept proposed by Kalil et al.[19] This latter hypothesis is supported by two of our results: (a) that transplant GNB group experienced a significantly lower incidence of septic shock as compared to the nontransplant GNB group, and (b) our preliminary cytokine and chemokine results.

To our knowledge, this is the first report to describe cytokine and chemokine levels in bacteremic solid organ transplant recipients. Importantly, we found that pro-inflammatory cytokines IL-2, IL-8, IL-15, IFN-α, and the monocyte chemoattractant MIP-1β were significantly lower in transplant vs nontransplant patients with GNB. We suspect that immunosuppressive medication used in the transplant group is at least in part responsible for the lower marker levels in the transplant GNB group. After adjusting for source of infection, immunosuppressive class, duration of symptoms, and presence or absence of septic shock, a statistically significant relationship remained between transplant status and IL-2 concentration. This suggests that during GNB, transplant recipients appear to exhibit a lower pro-inflammatory state than nontransplant recipients.

None of the aforementioned cytokine and chemokine levels differed significantly based on transplant status in patients with SAB, likely reflecting fundamental differences in the immunopathogenesis of SAB and GNB.[20] RANTES was the only cytokine that was significantly different between transplant and nontransplant recipients with SAB, and was in fact higher in the transplant recipients than in nontransplant recipients. After adjusting for source of infection, immunosuppressive regimen, septic shock, and duration of symptoms,

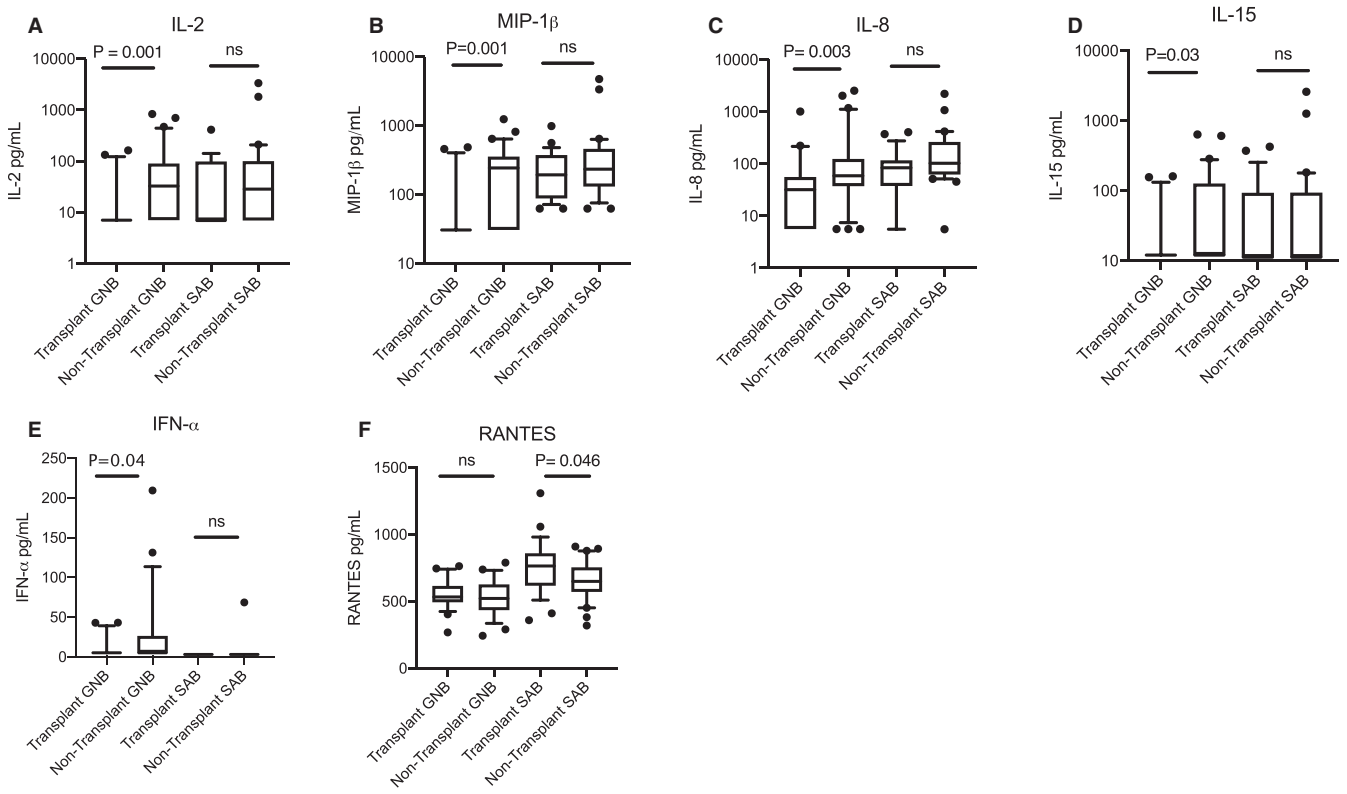

FIGURE 2 (A–F) Cytokine and chemokine levels differ by transplant status in patients with gram-negative bacteremia and *S. aureus* bacteremia. GNB, gram-negative bacteremia; SAB, *S. aureus* bacteremia; ns, not significant. Box plot extends from 25th to 75th percentile. The line in middle of box denotes median. Whiskers extend to 10th and 90th percentile. *p*-values were determined using Wilcoxon rank sum tests. Analyte concentrations below the lower limit of quantitation were replaced with one-half of the lower limit of quantitation. Thus when multiple patients had cytokine levels below the limit of detection, the first and third quartiles were identical to the median

this difference was no longer significant. RANTES is a pro-inflammatory chemokine that is known to be upregulated in response to *S. aureus*.[21] It is induced primarily by platelets, fibroblasts, $CD8^+$ T cells, and epithelial cells, and functions as a chemotactic agent to recruit leukocytes to the site of infection.[22] Our results suggest that despite immunosuppression, transplant recipients are capable of producing a robust pro-inflammatory response to SAB, akin to immunocompetent, nontransplant recipients.

The role of immunosuppression reduction during bloodstream infection is unknown.[23] Some investigators have suggested modification of the patient's immunosuppressive regimen (e.g., withholding the antimetabolite agent or reducing goal calcineurin inhibitor troughs) on the basis of a theoretical improvement in host immune response.[2,23-25] However, this practice may paradoxically increase the risk of harm, as reductions in immunosuppressants can increase the risk of allograft rejection and graft failure.[26] In the current study, a total of 20 transplant recipients underwent a reduction in immunosuppression due to bacteremia, however we were unable to conclude how this affected outcomes. Further studies need to evaluate whether immunosuppression in transplant recipients carries an increased risk of mortality during bacteremia.

While mortality was not significantly different in transplant and nontransplant recipients with bacteremia, the epidemiology of these infections differed substantially among the two populations. All of the transplant recipients developed health care-associated bacteremia while significantly fewer nontransplant recipients developed health care-associated bacteremia. This difference likely reflects the ongoing contact that transplant recipients have with the health-care system. Additionally, the exclusion of hemodialysis-dependent patients from the nontransplant cohort may account for part of this difference. Nevertheless, our findings highlight that transplant patients with indwelling central catheters are a particularly vulnerable population for SAB and underscores the importance of removing intravascular catheters whenever possible.

Transplant recipients with SAB developed AKI significantly more frequently than matched patients without transplantation. This trend was seen among those receiving known nephrotoxic immunosuppressants such as calcineurin inhibitors as well as patients receiving calcineurin inhibitor sparing immunosuppressive regimens. Additionally, AKI did not occur with significantly greater incidence in kidney transplant recipients as compared to non–kidney transplant recipients and patients who did not undergo transplantation. While the reason for the higher rate of AKI among transplant recipients is unknown, a possible mechanism is sepsis leading to acute tubular necrosis. If our finding is validated, future studies should evaluate the utility of AKI as a biomarker for the severity of sepsis as compared to markers such as SIRS criteria which rely on factors that may

TABLE 5 Gamma regression (with log link) parameter estimates and 95% confidence intervals when modeling transplantation status on IL-2 GNB cytokine concentration

Gamma regression (with log link) parameter estimates and 95% confidence intervals when modeling transplantation status on IL–2 GNB cytokine concentration (*N* = 59)		
Covariates	**Estimate (95% CI)**	***p*-value**
Intercept	4.71 (3.86, 5.56)	<.0001
Transplantation status	−3.94 (−6.91, −0.97)	.009
Source of infection (reference = GU)	Reference	
GU		
Endovascular infection	−1.82 (−3.30, −0.33)	.02
GI	0.39 (−0.38, 1.16)	.32
Joint	−2.18 (−4.45, 0.09)	.06
Respiratory/lung	1.00 (−0.42, 2.41)	.17
Skin/soft tissue	−0.56 (−2.85, 1.73)	.63
Unknown	0.22 (−0.87, 1.33)	.69
Immunosuppressive regimen (reference = none)	Reference	
None		
Monotherapy (steroid)	1.18 (−0.68, 3.05)	.21
CNI + steroid or CNI + antimetabolite	2.74 (−0.76, 6.23)	.12
CNI + mTOR inhibitor + steroid	1.69 (−1.48, 4.87)	.30
CNI + antimetabolite + steroid	2.32 (−0.64, 5.28)	.12
Duration of symptoms (48 h or more) (reference: <48 h)	−0.57 (−1.28, 0.13)	.11
Septic shock	−0.82 (−1.69, 0.05)	.07

Abbreviations: GNB, gram-negative bacteremia; CI, confidence interval; GU, genitourinary; GI, gastrointestinal; CNI, calcineurin inhibitor.

be impaired in immunocompromised patients, including fever and leukemoid response.[1,27]

Our study used a large, unique biorepository from clinically well-characterized patients with bacteremia and matched transplant and nontransplant patients by age, race, gender, and bacterial species. Nonetheless, it had limitations. The overall sample size and the number of each type of organ transplant was small, limiting study power. Biological specimens were collected at a single acute phase time point instead of longitudinally over the course of the infection. It is possible that there is variability of cytokine concentrations within this initial 72-h time interval, and that timing of antimicrobial therapy may influence concentrations. Additionally, we were unable to assess when reduction in immunosuppression occurred relative to biological specimen collection, and thus unable to determine whether reduction in immunosuppression affected chemokine or cytokine levels and patient outcome. The generalizability of the findings may be limited to patients with bacteremia due to *S. aureus*, *E. coli*, and *K. pneumoniae*. Finally, because this was a hypothesis-generating study, we did not apply multiple testing corrections and these inference-based analyses should be completed in a larger, external validation dataset. It is important to note that the large number of analyses performed increases the risk of false positive findings.

5 | CONCLUSIONS

We present the first study to examine cytokine and chemokine levels in solid organ transplant recipients with bacteremia. Our results challenge the long-held belief that transplant status portends poorer outcomes in SAB and GNB. We provide evidence that mortality may not be linked to immunosuppression, and that transplant recipients experience a lower incidence of septic shock than nontransplant recipients during GNB. Larger studies are needed to validate our findings, to further elucidate the role of immunosuppression on host immune response to bacteremia in transplant recipients, and to determine how we may use that information to further improve the outcomes of sepsis in transplant recipients.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. VGF reports personal fees from Novartis, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Basilea, Affinergy, Janssen, xBiotech, Contrafect, Regeneron, Basilea, Destiny, Amphliphi Biosciences. Integrated Biotherapeutics; C3J, grants from NIH, MedImmune, Cerexa/Forest/Actavis/Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Cubist/Merck; Medical

Biosurfaces; Locus; Affinergy; Contrafect; Karius; Genentech, Regeneron, Basilea, Janssen, from Green Cross, Cubist, Cerexa, Durata, Theravance; Debiopharm, Royalties from UpToDate; and a patent sepsis diagnostics pending. The other authors have no conflict of interests to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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