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ORIGINAL ARTICLE

Limited utility of blood cultures in the management of febrile outpatient kidney transplant recipients

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Abstract *Background/Purpose:* Blood cultures for patients suspected of having bacteremia are standard practice, although several studies demonstrate that blood cultures have limited utility because of a low true-positive rate and infrequent resultant changes in antibiotic treatment. However, most reports exclude immunocompromised patients such as transplant recipients. We assessed the utility of blood cultures in transplant recipients hospitalized for community-acquired infections and evaluated clinical characteristics to predict bacteremia.
Methods: This retrospective study included 136 febrile cases in 97 kidney transplant recipients admitted to our hospital for whom blood cultures were performed between February 2001 and March 2013.
Results: Among the 136 cases, blood cultures were positive, contaminated, and negative in seven (5.1%) cases, 12 (8.8%) cases, and 117 cases (86.1%), respectively. All bacteria detected in the seven cases were sensitive to the initial empirical antibiotics. Antibiotic treatment was changed based on the blood culture results only in one case for which the coverage was narrowed. The white blood cell count and C-reactive protein level were significantly higher in the patients with bacteremia. The predictive model based on these two factors successfully identified the high-risk group with a sensitivity and specificity of 86% and 91%, respectively.
Conclusion: Among the outpatient kidney transplant recipients, positive blood cultures were uncommon and scarcely affected antibiotic therapy, especially in patients with upper respiratory tract or urinary tract infections. Therefore, it may be reasonable to perform blood

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cultures only for patients with marked leukocytosis and high C-reactive protein level, even among transplant recipients.

Introduction

Transplant recipients are immunocompromised patients who receive several kinds of immunosuppressive drugs, which makes them susceptible to infection. Therefore, they are likely to require inpatient hospital care for the treatment of community-acquired infections during long-term post-transplantation follow up. Taking blood cultures of patients suspected of having bacteremia is the standard practice. Several guidelines recommend performing blood cultures for patients with community-acquired infections, especially pneumonia.[1–4] However, no well-designed randomized studies actually support these recommendations. Furthermore, several studies demonstrate that blood cultures have limited utility because of the low true-positive rate and infrequent resultant changes in management.[5–17] However, most of those reports exclude immunocompromised patients such as transplant recipients.[6,7,12–14,18–20] Several studies describe the incidence of bacterial infections in febrile outpatient pediatric transplant recipients,[21,22] although the actual utility of blood cultures for transplant recipients with community-acquired infections remains unknown.

Solid organ transplantation is a general treatment, and the number of transplant recipients is increasing. As a result, febrile transplant recipients are frequently examined in any emergency department. Since 1976, approximately 700 kidney transplantations have been performed in our hospital. Most transplant recipients have been followed at our outpatient department. During the long-term follow up of organ transplant recipients, community-acquired infections are a common and significant cause of patients requiring inpatient hospital care. Transplant recipients with infections were examined and treated in cooperation with a pulmonologist and infection control doctors in our hospital. Among kidney transplant recipients, the empiric therapy is penicillin and cephem antibiotics because of their safety and usability.

It is extremely important to know if and for whom blood cultures should be performed. Therefore, in this study, we assessed the utility of blood cultures for febrile outpatients who have received kidney transplants, and we created a predictive model to determine if the clinical characteristics of these patients influence the blood culture results.

Methods

Study population

We retrospectively identified 299 post-transplant patients who required inpatient hospital care and had at least one blood culture drawn in our hospital between February 2001 and March 2013. Fever was defined as a body temperature of $\geq 38^{\circ}C$. We excluded patients for whom blood cultures were drawn 24 hours after the admission ($n = 155$) and patients who had a body temperature $< 38^{\circ}C$ ($n = 8$). One hundred and thirty-six febrile cases of community-acquired infections among 97 kidney transplant recipients were ultimately included. The local institutional internal review board approved this study.

Blood cultures and definitions

Among the included cases, all blood cultures were obtained from patients in the outpatient department or within the 1st day after hospital admission. The cultures were tested by the Oxoid Signal Blood Culture System (Oxoid, UK). The results of blood cultures were classified as "positive," "negative," or "contaminated." Specimens were considered contaminated if bacteria from normal skin flora (e.g., *Staphylococcus epidermidis*) was detected and the experienced clinicians and infection control doctors evaluated the result as contamination. Contamination was considered a negative result. Pneumonia was defined as the presence of a new pulmonary infiltrate. Upper respiratory tract infection was defined as the presence of cough or sore throat without abnormal chest X-ray findings.

Immunosuppressive regimens

Maintenance immunosuppressive treatment consisted of one to three drugs such as prednisolone, a calcineurin inhibitor (e.g., tacrolimus or cyclosporine), and antimetabolic agents (e.g., mycophenolate mofetil, mizoribine, or azathioprine).[23]

Statistical analysis

The statistical significance of normally distributed, skewed, and dichotomous data was determined by using the Student *t* test, Wilcoxon signed rank test, and Fisher's exact test, respectively. Primary analysis was performed to assess the positivity rates of blood cultures and resultant changes in antibiotic treatment. Secondary analysis was meanwhile performed to identify the group at high risk of bacteremia by comparing the characteristics of patients with and without bacteremia. Predictive discrimination for positive blood cultures was assessed by receiver-operating characteristic (ROC) curve analysis based on maximizing sensitivity and specificity. All analyses were performed using JMP Pro 11 (SAS Institute, Cary, NC, USA). The level of significance was set at $p < 0.05$.

Results

Table 1 shows the baseline characteristics of the 97 transplant recipients from whom 136 blood cultures were drawn during the study period. Among these 136 cases, blood cultures were positive, contaminated, and negative in seven (5.1%) cases, 12 (8.8%) cases, and 117 (86.1%) cases, respectively. At the assessment of the blood cultures, the median time since transplant was 79 months (range, 2–370 months). None of the infections had developed in health care settings. No indwelling catheter or stent was inserted in any patient.

Table 2 shows the blood culture results, according to the infection source. The cases of bacteremia that involved urinary tract infections and enteritis were caused by *Escherichia coli*, and one case of pneumonia was caused by penicillin-susceptible *Streptococcus pneumoniae*. Bacteremia was not detected in any patient who developed upper respiratory tract infections. All bacteria were sensitive to nearly all antibiotics, including penicillin and cephem antibiotics, which are usually used as the empiric therapy in our hospital. Blood culture results prompted a change in empiric antibiotics in only one patient with suspected pneumonia: a broad-spectrum penicillin was changed to a narrow-spectrum cephem antibiotic. The antibiotics were changed in three cases, regardless of the blood culture results: a narrow-spectrum penicillin was changed to a broad-spectrum penicillin because of delayed recovery in two patients, and a broad-spectrum penicillin was changed to a carbapenem drug because of deterioration in a patient's condition. In the latter circumstance, the patient was diagnosed as having meningitis and died 40 days after admission, although the bacteria detected were sensitive to the empiric antibiotics.

Table 3 shows the characteristics of the patients with positive and negative blood cultures. The white blood cell (WBC) count and C-reactive protein (CRP) level were significantly higher in patients with positive blood cultures than in patients with negative blood cultures ($p < 0.005$). There were no differences between patients with positive and negative blood cultures with respect to age, sex, or immunosuppressive treatment. Therefore, we further evaluated a predictive model for bacteremia, based on the WBC and CRP levels. The ROC curve analysis produced WBC count and CRP level cut-off values of 15,800/μL and 125 mg/L, respectively. The sensitivity and specificity of the WBC count cut-off for predicting bacteremia were 86% and 75%, respectively, whereas those of the CRP cut-off level were 86% and 85%, respectively. The predictive model based on the two risk factors successfully stratified febrile transplant recipients in accordance with the risk of bacteremia, and identified patients at high risk of bacteremia with a sensitivity, specificity, positive predictive value, and negative predictive value of 86%, 91%, 35%, and 99%, respectively (Table 4).

Table 1 Baseline characteristics of 97 kidney transplant patients.

Variable	Patients (n = 97)
Age at transplantation (y)	34.6 (13.7)
Sex (M/F)	(63/34)
Donor age (y)	52.2 (11.9)
Donor sex (M/F)	(30/67)
Duration from KTx to BCs (mo)	79 (2–370)
Duration of dialysis (mo)	13 (0–292)
ABO incompatible	7 (7%)

Continuous data are presented as the mean (standard deviation) or median (range).
BCs = blood cultures; KTx = kidney transplantation.

Table 2 Rate of positive blood culture results and bacteria isolated from patients, based on infection.

Infection source	Positivity rate, n/N (%)	Bacteria
Urinary tract infection	2/36 (5.6)	*Escherichia coli*
Upper respiratory tract infection	0/35 (0)	
Pneumonia	1/20 (5.0)	*Streptococcus pneumoniae* (PSSP)
Enteritis	1/14 (7.1)	*E. coli*
Meningitis	1/2 (50)	*Streptococcus* spp.
Cellulitis	0/3 (0)	
Other/unknown	2/26 (7.7)	*Staphylococcus aureus* (MSSA), *Streptococcus agalactiae* (Group B)

MSSA = methicillin-susceptible *Staphylococcus aureus*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*.

Table 3 Clinical characteristics of patients with positive and negative blood culture results.

Variable	Positive (n = 7)	Negative (n = 129)	p
Age when examining blood cultures	46.6 (18.0)	44.0 (19.7)	0.737
Sex (M/F)	5/2	82/47	>0.99
Duration from KTx to BCs (mo)	129 (58–161)	77 (2–370)	0.224
Steroid withdrawal	1	9	0.422
Tacrolimus/cyclosporine	2/5	63/54	0.256
MMF/mizoribine/azathioprine	2/3/2	41/49/27	>0.99
White blood cell (count/μL)	19947 (6526)	12392 (6358)	0.003
C-reactive protein (mg/L)	228.8 (12.3–442.1)	37.7 (0–394.7)	0.004

Continuous data are presented as the mean (standard deviation) or the median (range).
BCs = blood cultures; KTx = kidney transplantation; MMF = mycophenolate mofetil.

Discussion

The main results of the present study were (1) positive blood cultures were rare in febrile transplant recipients

Table 4 Distribution of bacteremia stratified by the combination of the white blood cell count and C-reactive protein level.

	WBC count <15,800/μL *n*/*N* (%)	WBC count ≥15,800/μL *n*/*N* (%)	
CRP <125 mg/L	1/87 (1.1)	0/23 (0)	110
CRP ≥125 mg/L	0/9 (0)	6/17 (35.3)	26
	96	40	

CRP = C-reactive protein; WBC = white blood cell.

who developed community-acquired infections and required inpatient hospital care; (2) all bacteria detected by blood cultures were sensitive to the initial empiric therapy, and antibiotics were changed on the basis of blood culture results only in one (0.7%) case; (3) the WBC count and CRP levels were significantly associated with positive blood cultures and their combination may be helpful for identifying high- and low-risk patients with bacteremia.

The positivity and contamination rates were comparable with those previously reported in general febrile patients.[15,24] Immunocompromised patients have an increased risk of bacteremia and have been excluded from many published studies; however, the present results suggested that kidney transplant recipients who have received immunosuppressive drugs for a long time may not require special attention for the implementation of blood culture. The results of this study are consistent with reported results showing a bacteremia incidence of 0% among transplant patients without indwelling hardware.[22] Several studies report that bacteria resistant to empirical therapy are detected only in 0—1.0% of patients, including in patients with pneumonia,[5,7,9,18,25] pyelonephritis,[20,26] and cellulitis.[11,12,27,28] Consistent with previous reports, the present study indicates that blood culture results rarely prompt changes to empiric antibiotics.

Previous antibiotic use is associated with negative blood culture results.[29—32] Therefore, we performed a subgroup analysis by excluding 24 cases for which there was some possibility of the patients being administered some antibiotics. However, only 6% of blood cultures were positive, and changes in management were rare (0.9%) even in this subgroup.

Even in patients in whom true bacteremia was detected, changes to the narrow-spectrum antibiotics on the basis of the blood culture results were rarely made, which was consistent with previous reports.[5,7,15,33] This finding is partly because most patients had already recovered from their infections by the time blood culture results were reported. We usually administer penicillin or cephem as an empiric antibiotic. The penicillin and cephem used in our hospital is inexpensive, and its spectrum is not as broad as that of carbapenem. Therefore, even in patients for whom antibiotics were changed to narrower spectrum antibiotics such as narrow-spectrum cephalosporin, the cost-effectiveness and suppression of drug-resistant infectious microorganisms are questionable.

In this study, all blood culture results for patients with upper respiratory tract infections and cellulitis were negative, which is consistent with previous reports,[12,14,28,34] indicating that blood cultures have limited utility for these types of infections. Furthermore, the blood culture was positive in only one of 14 (7.1%) patients with enteritis. In this patient, *E. coli* was detected, which is part of the normal bacterial flora in the digestive tract. This finding further brings the utility of blood cultures into question.

With regard to urinary tract infections, two cases of bacteremia were detected. However, previous studies reveal that the high sensitivity of urine cultures for detecting the causative bacteria saves time and labor, compared to blood cultures.[15,20,26] Therefore, the utility of blood cultures for urinary tract infections is also limited. The rate of bacteremia in the cases of pneumonia was 5.0%, which is consistent with previous studies.[5,7,9,13] Patients with positive blood culture results were treated only with empiric antibiotics and the patients promptly recovered, which indicated that the utility of blood cultures for pneumonia may be limited. In this study, only two of 136 febrile patients developed meningitis. One of the two patients had bacteremia; however, the sample size in this subgroup is too small to draw any meaningful conclusions. If meningitis is strongly suspected, cerebrospinal fluid culture has an optimal diagnostic yield.[15] Therefore, the utility of blood cultures may be unclear.

To avoid performing blood cultures for patients with a low chance of yielding a positive result, several studies suggest implementing laboratory values as predictors of bacteremia. Chirouze et al[35] demonstrated the superiority of procalcitonin to other laboratory values as a predictor of bacteremia. By contrast, Ugarte et al[36] indicated the superiority of CRP. Procalcitonin was not routinely examined in the present patients; therefore, we could not assess the superiority of the aforementioned laboratory values as predictors of bacteremia. Some inflammatory mediators such as procalcitonin may be better predictors of bacteremia than the WBC count or CRP level, although it is not always feasible to inspect more parameters to reduce the number of blood cultures performed. The WBC count and CRP level are traditional predictors of positive blood cultures and are widely checked in clinical settings. Therefore, utilizing the WBC count and CRP level to reduce the number of blood cultures is a readily accepted practice, although the optimal cut-off values of the WBC count and CRP level must be evaluated further.

The present study has several limitations that should be mentioned. There were few patients with positive blood culture results. Therefore, the validity of the cut-off levels of the WBC count and CRP level could not be fully evaluated. In addition, the diversity of the sources of infection made it difficult to examine the utility of blood cultures for specific infectious diseases. However, immunocompromised patients are less likely to present with signs and symptoms related to the inflammatory response to infection. Therefore, transplant recipients who present with only fever in clinical settings must be examined. In accordance with the inclusion criteria, patients with infections who did not have blood cultures were not enrolled in this study. The reasons for not obtaining blood cultures vary, although they likely reflect a lower suspicion of bacteremia. Therefore, the present results may in fact overestimate the utility of blood

cultures for febrile transplant recipients. Furthermore, this was a single-center study, and the results may not be applicable to other regions or populations. Despite these limitations, the present study suggests that blood cultures have limited utility for managing community-acquired infections in transplant recipients.

In conclusion, positive blood cultures were uncommon and rarely prompted alterations to antibiotic therapy among febrile outpatient transplant recipients. The emergence of antibiotic-resistant bacteria requires caution. However, the utilization of WBC counts and CRP levels could reduce the number of blood cultures obtained without impairing the quality of clinical management.

Conflict of interest

None declared.

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