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Clinical Manifestation, Distribution and Resistance of Pathogen Causing Bacteremias Following Solid Organ Transplantation: A Clinical Analysis of 149 Patients

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Investigate the clinical manifestations and determine the distribution and characteristics of drug susceptibility of pathogen causing bacteremias, and provide evidence for clinical anti-infection treatments after solid organ transplantation. One hundred ninety eight episodes of bacteremias occurred in 149 patients between January 2003 and February 2014. Retrospective analysis of the pathogens and their drug susceptibility characteristics was carried out using a BD microbiological assay system. We also collected clinical and laboratory data of the effected patients. The gram negative bacteria accounted for 59.1% of all pathogens (117/198). The most common gram negative bacillus was *Escherichia coli*, while for gram positive bacteria, the main bacillus was *S. aureus*. The gram negative bacteria were relatively sensitive to aminoglycosides and carbapenem, while the gram positive bacteria were sensitive to glycopeptides and oxazolidone. The clinical manifestations of bacteremias included high body temperatures, onset shortly after solid organ transplantation, as well as a high mortality rate. Though gram positive bacteria played an important role, most of the bacteremias were caused by gram negative bacteria. The rate of antibiotic-resistant cases was very high for both the gram negative and positive bacteria.

Key words: Solid organ transplantation; bacteremias; pathogen; resistance.

Bacteremias remain one of the most common infectious diseases in clinic, which occur suddenly with a high mortality occurence. Bacteremia-associated mortality rates range from 3% to 33% of heart, 10% to 52% of liver, 6% to 25% of lung, 6% to 44.4% of pancreas or simultaneous kidney-pancreas, and 2.5% to 11% of kidney transplant recipients [1-10]. Our study [11] reveals that 44.7% of the bacteria in BSIs were gram-negative, 29.1% were gram-positive and 22.3% were polymicrobial after kidney and liver transplantation.

There is little research regarding the clinical features of bacteremias and the distribution and drug-resistance of bacteremic pathogens after solid organ transplantation (SOT). To improve the success of SOT, it is very important to investigate the distribution and drug-resistance of pathogens among bacteremic SOT recipients. In this study, we summarize the culture and drug-resistance of the pathogens in order to make antibiotics to be used appropriately in SOT recipients with bacteremias.

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MATERIALS AND METHODS

Study Population and Clinical Isolates

This study was conducted at the Third Xiangya Hospital, Central South University (Changsha) and Zhongnan Hospital, Wuhan University (Wuhan), which are two tertiary university referral hospitals in China. During the study period (from January 1, 2003 to February 28, 2014), 198 isolates were obtained from 149 SOT recipients with bacteremias. All recipients enrolled were administered triple immunosuppressant drugs consisting of mycophenolate mofetil, cyclosporine or tacrolimus, and corticosteroids. Recipients were rapidly tapered to 20 mg of prednisone per day by seven days post surgery. This study was approved by the two hospitals' ethics committees. The average age of recipients at the onset of bacteremias was 43.15±12.95 (12-67) years.

Definitions

Bacteremias were defined by using criteria proposed by Centers for Disease Control and Prevention (CDC) [12]: The isolation of a bacterium other than normal skin flora (*diphtheroids*, *bacillus spp*, or *coagulase-negative staphylococcus*) in one culture with signs of infection or the isolation of a microorganism from at least two consecutive cultures correlated with signs of infection.

Microbiologic Studies

A 10-mL blood sample drawn under sterile conditions was injected into each bottle of a set of aerobic and anaerobic blood cultures. Blood samples were processed by the BACTEC 9120 blood culture system (Becton Dickinson, Cockeysville, MD, USA). Species identification for the bacteria was performed using the Vitek-2 system (bioMérieux, Marcyl'Etoile, France). Antimicrobial susceptibility was determined by the Kerby-Bauer disk diffusion method and the minimum inhibitory concentration (MIC) was measured by agar dilution in the National Committee for Clinical Laboratory Standards guidelines [13]. The production of ESBL was detected by the double-disk synergy test [14]. Intermediate susceptibility to the antibiotics was considered resistance.

Antibiotics

Aztreonam (ATM), piperacillin (PIP), cefoperazone/sulbactam (CFS), cefazolin (CZO), cefuroxime (CXM), ceftazidime (CAZ), cefepime (FEP), amikacin (AN), levofloxacin (LVF) and meropenem (MEM), doxycycline (DOX), and trimethoprim/sulfamethoxazole (SXT), penicillin (PEN), erythromycin (ERY), clindamycin (CC), vancomycin (VAN), rifampicin (RA), teicoplanin (TEC), and linezolid (LZD) were products of Oxoid, England. The powder of vancomycin and teicoplanin was purchased from Tongtai Co., Guangzhou, China.

RESULTS AND DISCUSSIONS

Clinical Manifestation

We elaborated the clinical manifestation of SOT recipients with bacteremias as follows: 1. Fever and abnormal blood pressure. Considering all patients in this study, almost all bacteremic recipients had a fever, and 88 recipients had temperatures of 39°C or greater. Serious infections, especially gram-negative infections, caused septic shock and multiple organ dysfunction. 2. Onset in the early period after SOT. The majority of all bacteremias (159/198) occurred within six months of the operation. About 73% of all episodes of bacteremias (144/198) occurred within three months and nearly 7% between three and six months in our study. 3. Poor nutrition and immune function. About 62% of patients (92/149) had a serum albumin level of < 35 g/L and about 66% of patients (98/149) had a lymphocyte count of $< 0.5 \times 10^9$ / L. 4. Recipients were more susceptible to bacteremias when they experienced renal dysfunction after transplantation. And 50.3% of patients (75/149) had a serum creatinine level of > 150μmol/L before bacteremias occurred. 5. Most bacteremias were secondary to other infections. Many of the patients with bacteremias had primary infections and the most common was respiratory tract corruption at 34.8% (69/198), followed by intra-abdominal/biliary focus of 29.8%, deep venous catheterization of 13.5%, intestinal, urinary tract and other sources of 10.1%, and unknown sources comprised 12.1%. 6. High mortality. There were 57 cases out of the 149 patients who died, equalling a mortality rate of 38.3%. The mortality rate reached as high as 53.8% (14/26) when bacteremia was caused by *acinetobacter baumann*.

Laboratory Data

1. White blood cells (WBC) increased substantially. The amount of WBC in 20.8%

of patients (31/149) with bacteremias was more than 20×10^9/L and the highest reached 58.79×10^9/L.

2. Platelets dropped markedly. The amount of platelets in 19.75% of patients with BSIs was less than 50×10^9/L and it decreased to 2×10^9/L in some cases.
3. C-reactive protein (CRP) and procalcitonin (PCT) were greatly elevated. The highest serum level of CRP was 85.8 mg/L and the highest serum level of PCT was more than 100 ng/mL.
4. Causative organisms were mainly gram negative bacilli and the opportunistic infection had a higher morbidity rate in SOT recipients than in the common population.

Classification of Pathogens

One hundred ninety eight microorganisms were responsible for bacteremias in our study. The causative pathogens comprised 117 gram-negative bacteria (59.1%) (28 *E. coli,* with 17 of them ESBL positive; 32 other *enterobacters* with 19 of them ESBL positive; 26 *acinetobacter baumanii*; 19 other *nonfermenters*; the other six gram negative bacteria and three of them ESBL positive), and 81 gram-positive bacteria (40.9%) (Twenty-eight *S. aureus*; 24 *Enterococcus spp*; 15 *S. coagulase-negative*; eight *Streptococcus spp* and six other gram-positive

Table 1. Classification and constituent ratio of bacteria

Bacteria	Strain(n=198)	Constituent ratio(%)
Gram-negative bacilli	117	59.1
Escherichia coli	28	14.1
Klebsiella	11	5.6
The other *enterobacters*	21	10.6
Acinetobacter baumanii	26	13.1
The other *nonfermenters*	19	9.6
The other negative bacilli	12	6.1
Gram-positive bacteria	81	40.9
S. aureus	28	14.1
Enterococcus spp	24	12.1
S. coagulase-negative	15	7.6
Streptococcus spp	8	4.0
The other positive bacteria	6	3.0

Table 2. Gram-negative bacilli on antibiotic resistance rate of twelve [n,(%)]

Anti-microbial	*E.coli* (28)	The other *entero-bacteria* (32)	*Acinetobacter baumanii* (26)	The other *non-fermentative* (19)	The other gram negative bacilli (12)	Total drug resistance rate (%)
MEM	2(7.1)	3(9.4)	15(57.7)	11(57.9)	2(16.7)	28.2
FEP	16(57.1)	13(40.6)	16(61.5)	9(47.4)	4(33.3)	49.6
CAZ	18(64.3)	15(46.9)	18(69.2)	7(36.8)	3(25.0)	52.1
PIP	26(92.9)	24(75.0)	19(73.1)	10(52.6)	3(25.0)	70.1
CXM	20(71.4)	22(68.8)	21(80.8)	8(42.1)	3(25.0)	63.2
CZO	25(89.3)	26(81.3)	22(84.6)	11(57.9	3(25.0)	74.4
AN	3(10.7)	10(31.3)	18(69.2)	5(26.3)	4(33.3)	34.2
LVF	17(60.7)	9(28.1)	17(65.4)	4(21.1)	2(16.7)	41.9
DOX	16(57.1)	16(50.0)	12(46.2)	8(42.1)	1(8.3)	45.3
SXT	17(60.7)	14(43.8)	19(73.1)	8(42.1)	1(8.3)	50.4
CFS	14(50.0)	14(43.8)	9(34.6)	7(36.8)	2(16.7)	39.3
ATM	18(64.3)	15(46.9)	21(80.8)	9(47.4)	4(33.3)	57.3

bacteria), as shown in Table 1.

Drug-Resistance of Gram Negative Bacilli

The drug resistance of gram-negative bacilli from the highest to the lowest occurrences were first generation cephalosporin, semisynthetic penicillins, second generation cephalosporins, monocyclic beta lactam, third generation cephalosporin, sulfonamides, fourth generation cephalosporins, tetracycline, quinolone, third-generation cephalosporins/ Sulbactam, aminoglycoside, and antibiotics (Table 2).

Table 3. Gram-positive cocci on antibiotic resistance rate of ten [n, (%)]

Antibacterial agents	*Staphylococcus aureus* (28)	*Enterococcus spp* (24)	*Coagulase negative staphylococcus* (15)	The other poitive bacteria (14)	Total drug tolerance rate (%)
ERY	23(82.1)	22(91.7)	14(93.3)	12(85.7)	87.6
VAN	0(0.0)	1(4.2)	0(0.0)	5(35.7)	7.4
CC	19(67.9)	23(95.8)	8(53.3)	13(92.9)	77.8
LVF	14(50.0)	20(83.3)	10(66.7)	13(92.9)	70.4
SXT	22(78.6)	22(91.7)	12(80.0)	12(85.7)	84.0
AN	7(25.0)	16(66.7)	8(53.3)	11(5.6)	51.9
PEN	25(89.3)	17(70.8)	13(86.7)	14(100.0)	85.2
RA	3(10.7)	19(79.2)	6(40.0)	7(50.0)	43.2
TEC	0(0.0)	0(0.0)	0(0.0)	4(28.6)	4.9
LZD	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.0

Drug Resistance of Gram-Positive Bacilli

The drug-resistance of gram-positive bacilli from the highest occurence to the lowest were macrolides, penicillin, sulfonamides, lincosamides, quinolone, aminoglycoside, rifampicin, peptides, and oxazolidinone antibiotics (Table 3).

DISCUSSION

Bacteremia is still a dangerous factor threatening the success of SOT. In the present study, the main pathogen causing bacteremias were gram-negative bacteria (59.1%) after SOT in both hospitals investigated over a ten year period, which is consistent with foreign data [15-17]. The most common bacteria causing bacteremias were *E. coli*, *S. aureus*, *acinetobacter baumannii*, and *Enterococcus spp* after SOT.

The most common gram negative bacilli were *E. coli* (14.1%), followed by *acinetobacter baumannii* (13.1%). Opportunistic pathogens, such as *Agrobacterium cradiabacter*, *Ochrobactrum anthropi*, *Flavobacterium a*nd *Serratia rubidaea*, were common, suggesting that the immune functions of SOT patients were extremely weak. Long-term immunosuppressants and broad-spectrum antibiotics were administered, and various indwelling tubes were used after SOT, which caused a higher rate of opportunistic infection.

The drug susceptibility tests showed that the sensitivity of gram-negative bacilli to semi-synthetic penicillins, sulfonamides and first- to third- generation cephalosporins dropped significantly (drug resistance rate > 50%). In our study, 61% of *E. coli* and 59% of other *enterobacters* produced ESBL, indicating that the ESBL-producing bacteria have become a complex clinical problem.

The sensitivity of gram-positive bacteria to macrolides, penicillin, sulfonamides, lincosamides, quinolones and aminoglycosides dropped significantly (drug-resistance rate>50%), and the drug-resistance rate to macrolides, penicillin, sulfonamides, lincosamides and quinolones was more than 70%. These gram positive bacteria were only sensitivite to glycopeptide and oxazolidinone, which was consistent with previous reports [18].

We found that bacteremias after SOT had high morbidity and mortality rates, and the pathogen causing bacteremias had strong drug-resistances. The possible explanation to this may

be the fact that nosocomial infections and pathogen resistance are on the rise throughout the world.

It is more important to prevent the bacteremia than to treat it. Pathogen-causing bacteremias following SOT have strong drug resistances and the effect of anti-infection medications is poor. According to the clinical and laboratory features of bacteremias after SOT and the distribution of pathogens, we can choose effective antibiotics in patients with suspected bacteremias while awaiting for the results of blood cultures.

Some solutions, such as strictly limiting the use of intravascular catheters, removing unnecessary catheters as soon as possible, shortening the course of antibiotic treatments, and preventing cross-infections can effectively reduce the occurrence of bacteremias. If a serious bacterial infection occurs in patients after SOT, reducing the use of immunosuppressants and changing the prophylactic regimen of antibiotics according to bacterial drug resistant spectrums can help prevent the development of bacteremias and drug-resistance of bacteria.

CONCLUSIONS

The clinical manifestations of bacteremias included high body temperatures, onset shortly after solid organ transplantation, as well as high mortality rates. Although gram positive bacteria played an important role, most of bacteremias were caused by gram negative bacteria among SOT recipients. The antibiotic resistance rate of gram negative bacteria was very high, as was the case with gram positive bacteria.

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