

Profile and Antibiotic Pattern of Blood Stream Infections of Patients Receiving Hematopoietic Stem Cell Transplants in Southwest China

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Background: Bloodstream infection (BSI) is a serious medical issue causing non-relapsed mortality in patients receiving hematopoietic stem cell transplantations (HSCT).

Methods: The characteristics of all patients receiving HSCT (autologous and allogeneic HSCT) in our hospital from 2013 to 2019 were studied. Ratios, medians, and ranges were calculated to describe categorical variables. Chi-square tests were performed to compare the difference between ratios.

Results: A total of 741 patients receiving 746 HSCT procedures—including 376 allogeneic, 370 autologous, and four of both types—were included in the study. The overall incidence of BSI in post-transplantation patients was 8.8% (N = 65). Gram-negative bacteria were the most common strains each year (33.3–81.3%), and *E. coli* was the most frequently isolated (33.3%). *Enterobacteriales* represented 64.9% of multidrug-resistant (MDR) bacteria, and the ratio of MDR rebounded from 25% to 100% within a year. A total of 27 patients died from BSI after HSCT, and the seven-day and 30-day death tolls were 12 and 18, respectively. MDR caused 63% of deaths among patients with BSI and the mortality rate caused by tigecycline-resistance was as high as 100%.

Conclusion: Our results reveal the changing epidemiology of BSI and antibiotic resistance in patients receiving HSCT in Southwest China, as well as showing that MDR and tigecycline-resistant microorganisms should be given more attention. Thus, long-term routine microorganism epidemiological and resistance monitoring in patients undergoing HSCT should be a vital practice in future.

Keywords: bloodstream infection, hematopoietic stem cell transplantations, multidrug-resistant bacteria

Introduction

Infection is one of the most common complications causing transplantation failure and non-relapse mortality (NRM) in hematological malignancy patients after hematopoietic stem cell transplants (HSCT).¹ Bloodstream infection (BSI) is a high risk and is related to incidence and NRM rates, with BSI rates ranging from 13% to 55.8%, and NRM ranging from 24% to 43.6%.^{2–8} Therefore, an in-depth understanding of the characteristics of BSI in patients receiving HSCT is necessary. Since the 1960s, the major pathogen type implicated in BSI has shifted from gram-negative bacteria (GNB) to gram-positive bacteria (GPB) and back again.^{6,9–11} This trend has continued into the 21st century, to the extent, that GNB has again become the main pathogen of BSI.^{4,12,13}

Furthermore, multidrug-resistant (MDR) bacteria and extensively drug-resistant (XDR) bacteria have become an increasing global concern,¹⁴ representing significant challenges to the medical profession. The problem is more prominent in patients undergoing HSCT due to the extended use of antibiotic prophylaxis and broad-spectrum antibiotics.^{4,15} According to available—but incomplete statistics—the quinolone resistance rate has increased to 86% in some countries, while the incidence of carbapenem resistance increases to 25% from the initial zero-resistance state in post-transplantation patients on average every year.^{4,6,16,17} The overall resistance rate of tigecycline—one of the last possible treatment options of antibiotics—has not been reported in China or abroad to date. Understanding the resistance

rate is important when choosing antibiotics, as trends in resistance profiles change annually and have a significant bearing on treatment outcomes.¹²

To date, the characteristics of post-HSCT BSI have been retrospectively investigated in the United States and various European countries at different times, but data about BSI after HSCT in China is scarce, especially in Southwest China. Therefore, our study was designed to describe the frequency of BSI and antimicrobial susceptibility in patients receiving HSCT in our hospital from 2013 to 2019, with the aim of clarifying the epidemiology of BSI and the rates of resistance to antibiotics demonstrated after HSCT in Southwest China.

Materials and Methods

Patient Population

The study was designed to analyze BSI in patients during HSCT retrospectively at West China Hospital from 2013 to 2019. All patients older than 14 who underwent HSCT were included. In our study, each year was analyzed as a separate period, and BSI data for different years were compared. Certain characteristics of all patients were noted, including demographics, underlying disease, transplant type, BSI episodes, infection sites, antimicrobial susceptibility, and survival. Incidence was calculated according to the positive rate of blood culture episodes per the annual number of transplants, excluding positive results related to the catheter and occurring before HSCT. As the study was performed with retrospective resources but did not involve active human participants or tissue, the Institutional Review Board of West China Hospital waived the need to obtain ethics approval and patient consent. This study complies with the Declaration of Helsinki. All methods were implemented following the relevant guidelines and regulations.

Definitions

HSCT-associated BSI was defined as isolates of bacteria or fungi from blood culture occurring during transplantation. This included commensal flora—such as coagulase-negative *staphylococci* (CoNS) and some fungi on the skin, which are harmful to patients with severe neutropenia—and excluded catheter-related sample contamination. BSI-associated mortality was defined as death occurring after a positive blood culture during the same hospitalization period. If two or more pathogens were found in a single blood culture, it was defined as polymicrobial. An unknown or endogenous infection source was recorded when no other positive examination results or physical signs for infection presented except blood culture. All patients received prophylactic antibiotic treatment before transplantation. Blood culture was conducted when body temperature surpassed 38 degrees or shivering occurred, and empirical antibiotic treatment protocols were developed immediately according to the international febrile neutropenia guidelines.^{18,19} Furthermore, antibiotics were adjusted according to the results of antimicrobial susceptibility testing if the infection symptoms were not alleviated; otherwise, the antibiotics were used continuously. MDR, XDR, and pan- drug-resistant (PDR) bacteria were classified based on the standardized international terminology created by the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention.²⁰ The incidence of drug resistance was calculated by resistance strains/all isolates. Outcomes for patients were not statistically analyzed in our study; we simply assessed the mortality at seven days and 30 days after BSI was recorded.

Statistical Analysis

Ratios, medians, and ranges were calculated to describe categorical variables. Chi-square or Fisher's exact tests were performed to compare the difference between ratios. All *p* values in our study were two-sided, and *p* < 0.05 was considered significant. All analyses were conducted with SPSS (version 24.0, SPSS, Inc, Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA) software.

Results

Characteristics of Patients

From January 2013 to December 2019, a total of 741 patients received 746 HSCT procedures, including 376 allogeneic (50.4%), 370 autologous (49.6%), and four of both types (0.5%), with an increasing number reported every year. The median

patient age was 40 (range: 14–66), and 426 of the patients were male (57.1%). Acute myeloid leukemia (AML) and non-Hodgkin's lymphoma (NHL) were the most common underlying diseases in allogeneic HSCT (allo-HSCT) and autologous HSCT (auto-HSCT), respectively (Table 1). Over the seven-year study period, 75 BSI episodes in 65 patients (8.8%) were recorded with isolated pathogenic microorganisms in blood culture. Out of the 65 patients, 52 were in allo-HSCT (80.0%), 12 in auto-HSCT (18.5%), and one was both (1.5%). The median age was 38 (range: 14–58) and 34 were male (52.3%). The most frequent baseline diseases remained AML in allo-HSCT and NHL in auto-HSCT. The period in which BSI occurred after HSCT ranged from 0 to 125 days (median: 13 days). Figure 1 showed the number of transplantations performed and BSIs recorded every year. The overall trend in the incidence of BSI shows a decrease, despite increasing HSCT. The main site of infection was pulmonary. Other information concerning patients with BSI is shown in detail in Table 1.

Microbiology and Resistance to Antibiotics

Information on microorganisms from 75 episodes and their progression are shown in Table 2. GPB, including CoNS, was isolated in 18 episodes (24.0%), GNB in 49 (65.3%) episodes, and fungi in 8 (10.7%) episodes. No difference could be observed in the incidence of any kind of microorganisms across the years analyzed ($p = 0.669$). GNB was the main pathogen causing BSI per year, and in this category, *E. coli* was the most frequently isolated, followed by *P. aeruginosa*. Among GPB infections, *Enterococcus* spp. was the most frequently detected, followed by *staphylococcus* spp. The eight

Table 1 Characteristics of Patients After HSCT

Characteristic	All Patients N = 741 (%)	Patients with BSI N = 65 (%)
Gender		
Female	315 (42.5%)	31 (47.7%)
Male	426 (57.5%)	34 (52.3%)
Age		
Median	40	38
Range	14–66	14–58
Disease		
AML	199 (26.7%)	21 (32.3%)
ALL	120 (16.1%)	15 (23.1%)
AUL	6 (0.8%)	3 (4.6%)
HL	26 (3.5%)	0
NHL	174 (23.3%)	6 (9.2%)
CML	25 (3.4%)	4 (6.2%)
AA	38 (5.1%)	6 (9.2%)
PNH	4 (0.5%)	0
MDS	40 (5.4%)	4 (6.2%)
MM	93 (12.5%)	4 (6.2%)
POEMS	13 (1.7%)	0
Others	8 (1%)	2 (3%)
Type of HSCT		
Allo-HSCT	376 (50.4%)	52 (80%)
Auto-HSCT	370 (49.6%)	12 (18.5%)
Both	4 (0.5%)	1 (1.5%)
Site of infection		
Pulmonary	/	41 (63.1%)
Gastrointestinal tract	/	14 (21.5%)
Skin and soft tissue	/	3 (4.6%)
Endogenous/Unknown	/	7 (10.8%)

Abbreviations: BSI, bloodstream infection; HSCT, hematopoietic stem cell transplant; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; AUL, Acute undifferentiated leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; CML, chronic myeloid leukemia; AA, aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; MDS, myelodysplastic syndromes; MM, multiple myeloma; Allo-HSCT, allogeneic hematopoietic stem cell transplant; Auto-HSCT, autologous hematopoietic stem cell transplant.

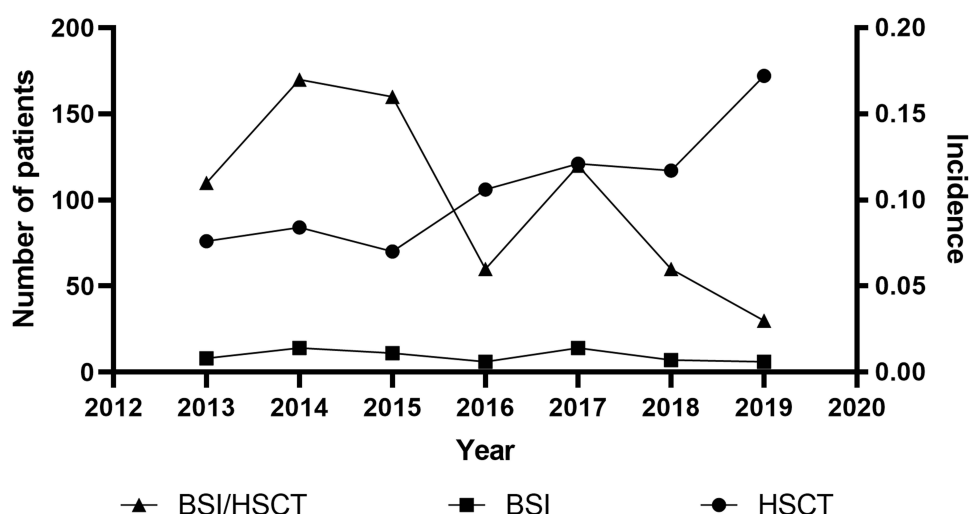


Figure 1 The incidence in HSCT patients and overall episodes throughout the years.

fungi isolates included *Candida tropicalis* ($N = 3$), *Candida krusei* ($N = 2$), *Trichosporon japonicum* ($N = 1$), *Fusarium* ($N = 1$), and an untyped strain ($N = 1$).

Of the 75 episodes, 67—including 61 bacteria and 6 fungi—were tested for antimicrobial susceptibility (another eight patients died before blood culture results became available). A total of 37 episodes were MDR (55.2%) and 11 were XDR (16.4%); no PDR cases were recorded. The ratios of MDR for each year are shown in Figure 2. Notably, the incidence of MDR tended to rebound despite decreasing BSI, especially in 2019, where all BSI causes were identified as MDR or XDR bacteria. *Enterobacterales* and *Enterococcus* were reported as the highest frequency infections for MDR or XDR cases among GNB and GPB, respectively. The resistant isolates are shown in Table 3. Additionally, the incidence of extended-spectrum β -Lactamase (ESBL)-producing *Enterobacterales*, carbapenem resistance, and tigecycline resistance was also significant, with the trends for these three types of resistance illustrated in Figure 3. The incidence of carbapenem resistance and tigecycline resistance per year, excluding natural resistance, ranged from 13.3% to 25.0% and from 0% to 12.5%, respectively, which included *E. coli* ($N = 4$), *K. pneumoniae* ($N = 3$), *P. aeruginosa* ($N = 2$),

Table 2 Changing Prevalence of BSI in Patients After HSCT

	2013	2014	2015	2016	2017	2018	2019	p value
GPB	1	4	3	1	4	2	3	0.725
<i>Enterococcus</i> spp.	1	1	2	1	2	0	2	0.624
<i>Streptococcus</i> spp.	0	2	1	0	0	0	0	0.556
<i>Clostridium</i> spp.	0	0	0	0	0	1	0	0.222
<i>Staphylococcus</i> spp.	0	1	0	0	2	1	1	0.916
GNB	5	10	13	5	8	6	2	0.534
<i>E. coli</i>	2	5	6	4	5	1	2	0.320
<i>P. aeruginosa</i>	1	2	1	1	1	1	0	0.989
<i>Klebsiella</i> spp.	0	0	4	0	2	0	0	0.130
<i>S. maltophilia</i>	1	1	1	0	0	2	0	0.494
<i>Acinetobacter</i> spp.	0	1	0	0	0	0	0	0.735
<i>Enterobacter</i> spp.	1	0	0	0	0	1	0	0.245
<i>Capnocytophaga</i> spp.	0	0	0	0	0	1	0	0.367
Fungi	2	1	0	1	2	1	1	0.630
Polymicrobial	0	1	4	1	0	2	0	0.188

Abbreviations: BSI, bloodstream infection; HSCT, hematopoietic stem cell transplant; GPB, gram-positive bacteria; GNB, gram-negative bacteria.

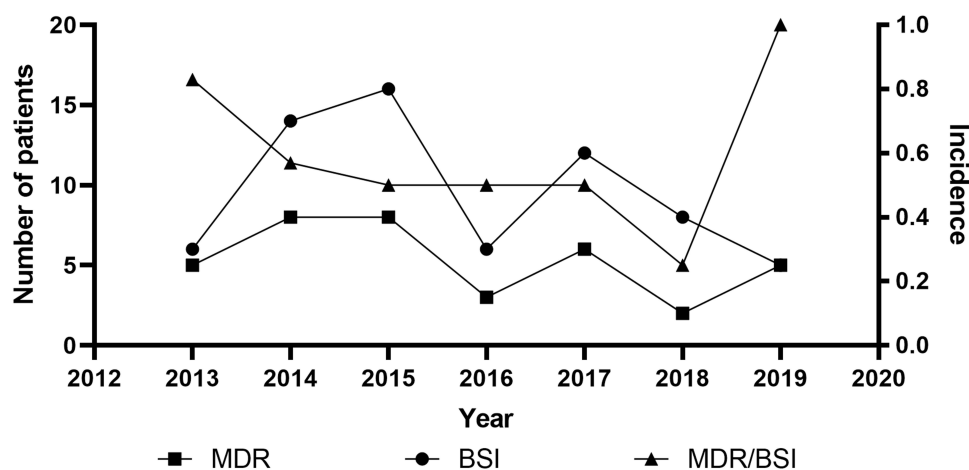


Figure 2 The incidence of MDR and overall episodes of MDR or BSI in different years.

E. Faecium (N = 2), and *A. baumannii* (N = 1) for carbapenem resistance, and *E. coli* (N = 2) and *K. pneumoniae* (N = 1) for tigecycline resistance (Table 4).

Outcomes for Post-Transplantation Patients with BSI

Despite a lack of detailed survival analysis to date, only 57 patients with BSI after HSCT were followed. The median time between BSI and death was nine days (range: 1–55 days). Of the 57 patients, 27 died from BSI, including 24 allogeneic and three autologous HSCT patients, 17 of whom were MDR or XDR. All tigecycline-resistant patients died, while 8 of 11 carbapenem-resistant patients died. Twelve patients died within seven days of BSI detection, and 18 patients died within 30 days of BSI detection (including the twelve patients died within seven days). MDR or XDR (N = 9) was the main cause of seven-day mortality. Three patients died of fungal BSI within 30 days. Seventeen patients with MDR or XDR remained alive. The resistance to antibiotics and outcomes is shown in Table 5.

Table 3 The Overall Distribution of MDR or XDR Microorganism

MDR	N = 37/58
<i>Enterococcus</i> spp.	4/9
<i>Enterobacteriaceae</i> spp.	24/30
<i>Pseudomonas aeruginosa</i>	3/7
<i>Acinetobacter</i> spp.	1/1
<i>Stenotrophomonas maltophilia</i>	3/5
<i>Staphylococcus</i> spp.	2/6
XDR	N = 11/58
<i>Enterococcus</i> spp.	2/9
<i>Enterobacteriaceae</i> spp.	6/30
<i>Pseudomonas aeruginosa</i>	1/7
<i>Acinetobacter</i> spp.	1/1
<i>Stenotrophomonas maltophilia</i>	0/5
<i>Staphylococcus</i> spp.	1/6

Abbreviations: MDR, Multidrug-resistant; XDR, extensively drug-resistant.

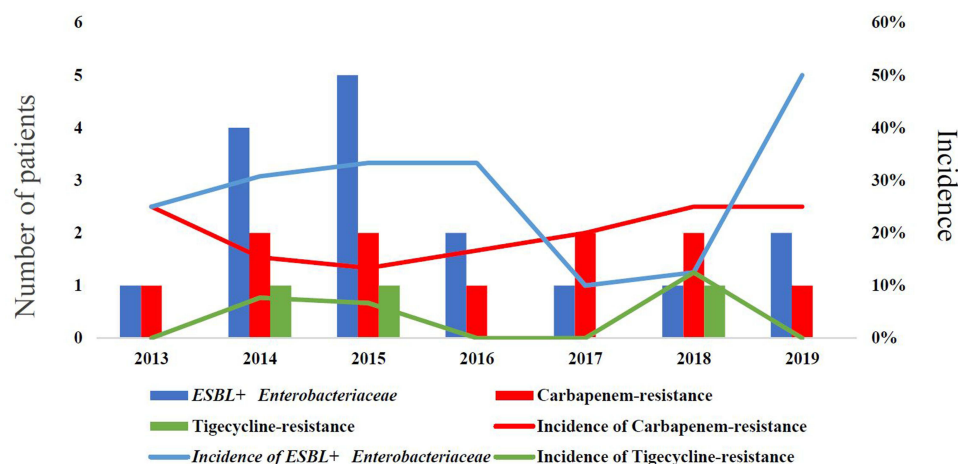


Figure 3 The changing incidence and number of ESBL, carbapenem resistance, and tigecycline resistance within the year.

Discussion

In our study, 8.8% (N = 65) of patients undergoing HSCT had isolated bacteria or fungi in blood cultures from 2013 to 2019. GNB was the common pathogen in BSI every year, and *E. coli* was most frequently isolated in post-transplantation patients. A total of 10.7% (N = 8) of patients with BSI had isolated fungus in blood samples, while 55.2% (N = 37) of patients with antimicrobial susceptibility tests were identified as MDR or XDR, with a decreasing trend over the study period. A total of 27 patients died of BSI, 12 of whom (including nine patients with MDR or XDR) died within seven days of BSI detection. A total of three patients with fungal BSI died within 30 days.

Since 2000, isolates of GPB have declined rapidly due to fewer catheter-related bacteria, and GNB has increased parallel to the rising rate of quinolone resistance,^{21,22} to the extent that GNB has gradually replaced GPB as the main isolate in blood culture.²³ The incidence of BSI decreased between 2013 and 2019 and GNB was the most common infection type in our study; these trends were consistent with the data reported in other countries and regions.^{4,24} *E. coli* and *Enterococcus*, both normal commensal bacteria in the human intestine, were the most frequently found GNB and GPB types in our study, respectively (the top pathogen in BSI after HSCT or high-dose chemotherapy is almost always reported to be *E. coli* or *Enterococcus*).^{12,15,24–26} Some researchers have reported that prolonged neutropenia and marked gastrointestinal mucositis caused by various types of conditioning regimens damage the phagocyte and the defensive

Table 4 Carbapenem- or Tigecycline-Resistance in Different Strains

	<i>E. coli</i> (N = 25)	<i>K. pneumoniae</i> (N = 6)	<i>P. aeruginosa</i> (N = 7)	<i>S. maltophilia</i> (N = 5)	<i>E. faecium</i> (N = 7)	<i>A. baumannii</i> (N = 1)
Carbapenem resistance	4	2	2	/	2	1
Tigecycline resistance	2	1	/	0	0	0

Table 5 Seven- and Thirty-Day Mortality of Different Antibiotics-Resistance

	7-Day Mortality (N = 12)	30-Day Mortality (N = 18)
MDR or XDR	9	14
Carbapenem-resistance	4	7
Tigecycline-resistance	1	3
Fungus	2	3

Abbreviations: MDR, Multidrug-resistant; XDR, extensively drug-resistant.

barrier, which facilitate normal commensal bacteria entering the blood.^{27,28} Furthermore, it was significant that fungi were isolated relatively often in our study: A total of eight patients (12.3%) were diagnosed with fungal BSI while 33 (2.8%) and two (2.25%) patients with fungal BSI were confirmed in Spain and East China, respectively.^{12,24} The warm, humid climate in Southwest China is beneficial to the growth and reproduction of fungi, which could cause a higher incidence of fungal infection in post-transplantation patients. Thus, antifungal therapy for patients after transplantation is an important consideration in similar climates.

MDR has already become a major medical challenge worldwide and it is particularly prominent in patients undergoing HSCT.^{14,24} However, studies have shown that the rate of MDR is declining.^{29,30} The rate declined in our study from 2013 to 2018, but the incidence of MDR in 2019 was substantially elevated. Furthermore, despite fewer BSI diagnoses, all patients were MDR, a finding which indicates that MDR microorganism monitoring cannot be relaxed. Since carbapenem is often used in patients with neutropenia and tigecycline is the last treatment option for anti-infective therapy in clinics, resistance to these two drugs is of particular concern. We found that *E. coli* and *K. pneumoniae* were the most prevalent causes of bacteria resistance to carbapenem or tigecycline. Additionally, they are reported to be the most common isolates in patients with repeated BSI.^{31–33} These two microorganisms evolve into MDR mainly owing to hydrolase caused by plasmid mutations during the long-term use of antibiotics.^{34,35} One or two episodes with carbapenem- or tigecycline-resistant BSI were recorded per year in our study, and the overall incidence of resistance to carbapenem and tigecycline were 18.3% and 5.0%, respectively. Published articles regarding carbapenem-resistance in transplant patients reported overall resistance rates of 15.8–25.0% in Central and East China and 17.0–44.0% in Western countries.^{4,15,16,24,36} Therefore, our data is consistent with local and international findings. To date, no studies have reported data on the incidence of tigecycline resistance in patients undergoing HSCT. Despite a resistance rate of only 5.0% and very low absolute quantity, tigecycline resistance should be studied further due to the very high mortality rate (100%) and the reports of cases each year. Another noteworthy risk is the incidence of ESBL+ *Enterobacterales*, which has been demonstrated an obvious upward trend over the last years, reminding doctors that antibiotics with β -Lactamase enzyme inhibitors are preferred in the treatment of BSI.

As this is a retrospective study, outcome data were analyzed simply. In line with the 30–50% mortality rates shown for patients with BSI in other studies,^{15,37,38} our study indicated a mortality rate of 47.4%. Since prolonged or severe neutropenia has been shown to be an independent risk factor for BSI mortality, we focused on the mortality rates at seven days and 30 days, which is when severe or prolonged neutropenia occurred in our study. The results showed rates of 17.9% and 26.9% at seven-day and 30-day periods, respectively, which was higher than the rates in other developed areas, both domestically and internationally.^{4,24} Advances in supportive care built on strong personal and collective economic circumstances have been shown to improve post-HSCT survival.³⁹ Hence, our short-term mortality rate was likely suboptimal, in part due to unfavorable personal economic status and national conditions. Additionally, it is acknowledged that BSI is associated with a poor prognosis for HSCT^{37,40,41} and that MDR or XDR bacteria are of key importance in determining a prognosis for BSI,^{15,42} especially carbapenem- and tigecycline-resistant pathogens. Notably, two patients died from fungal BSI in our study. One of these patients died on the day of transplant, with the antimicrobial susceptibility test revealing that no antibiotics were effective except amphotericin B. This indicated that fungal BSI could be fatal to transplant recipients.^{4,42}

Our study reported the BSI of patients after HSCT in Southwest China and reflected some regional characteristics. More importantly, this was the first reporting of data on tigecycline resistance in this area. However, our study had some limitations. First, the sample size was small, because all patients were from a single center where donor unavailability and economic difficulties were common for most patients. Second, this was a retrospective study. We reported observations based on historical data and were thus unable to perform a detailed analysis. Further, in-depth exploration of treatment factors, such as examination of the mechanisms of antibiotics resistance, could not be carried out. Third, the conditioning regimen, graft versus host disease (GVHD), comorbidities, and treatment for BSI were not included in the analysis. Therefore, it was difficult to perform a detailed survival analysis with any accuracy. Data from multiple hospitals could be included in future studies, including analysis of the factors outlined above.

Conclusion

To summarize, our study concluded that the epidemiology of BSI and antibiotic resistance in patients receiving HSCT were continually changing in Southwest China between 2013 and 2019. MDR-associated BSI was heavily associated with poor outcomes. Thus, long-term routine epidemiological and resistance monitoring for pathogenic microorganisms, especially MDR microorganisms, will be indispensable in future.

Abbreviations

BSI, bloodstream infection; NRM, non-relapsed mortality; HSCT, hematopoietic stem cell transplantations; MDR, multidrug-resistant; XDR, extensively drug-resistant; PDR, pan drug-resistant; GPB, gram-positive bacteria; GNB, gram-negative bacteria; ECDC, European Centre for Disease Prevention and Control; CDC, Centers for Disease Control and Prevention; AML, acute myeloid leukemia; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia; AUL, acute undifferentiated leukemia; HL, Hodgkin lymphoma; CML, chronic myeloid leukemia; AA, aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; MDS, myelodysplastic syndromes; MM, multiple myeloma; ESB, extended-spectrum β -Lactamase; GVHD, graft versus host disease.

Ethics Approval and Consent to Participate

As the study was performed with retrospective resources and not involving human participants and/or tissue, the Institutional Review Board of West China Hospital waived the need to obtain ethics approval and patient consent. This study complies with the Declaration of Helsinki.

Data Sharing Statement

The data and materials analyzed in our study are available from the corresponding author on reasonable requests.

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Disclosure

The authors report no conflicts of interest in this work.

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