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Letter to Editor

High Frequencies of Drug-resistant Pathogens in Blood Stream Infections Associated with Hematologic Disorders: Five-year Single Institutional Surveillance from 2010 to 2014

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Abstract

In order to improve the management of infectious complications associated with hematologic disorders, we conducted a retrospective 5-year analysis of Blood Culture (BC) tests obtained from febrile patients with hematological disorders treated in our institute between 2010 and 2014. BCs were performed using the BacT/ALERT 3D system (bioMérieux, Marcy l'Etoile, France) and identification and antibiotic susceptibility testing were performed using VITEK2 (bioMérieux). In 8,549 BC tests obtained from 1,517 febrile events, 325 BC tests showed positive results in 154 febrile episodes with 91 patients. In BC-positive episodes, the incidence of BC-positivity for 3 consecutive BC tests per febrile episode was 98.1 %. The frequencies of Gram-positive and Gram-negative bacteria as the causative pathogen were almost equal (44.5 % *vs* 43.3 %). The frequency of drug-resistant bacteria, such as either methicillin-resistant cocci or extended spectrum beta-lactamase producing organism, was more than 50 %. The use of a central venous catheter showed a positive relationship with the methicillin-resistant cocci in our series. Our study found increasing frequencies of drug-resistant bacteria as the pathogens of blood stream infection in hematological disorders. These results are instructive for the appropriate selection of empiric antibiotic therapy for febrile events in patients with hematologic malignancies.

Keywords: Infection; Blood culture test; Hematologic disorder; Febrile neutropenia; Drug-resistant bacteria

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Introduction

Despite the recent progress in supportive management with therapy for hematologic disorders, infections with microorganisms, such as pneumonia or Blood Stream Infection (BSI), still remain as frequent and serious complications. Chemotherapy-induced neutropenia is a major risk factor for infection-related morbidity and mortality, and Febrile Neutropenia (FN), which is a fe-

brile event where the patients has an absolute neutrophil count of less than 0.5 x 10^9/L, has been one of the most serious, occasionally fatal, complications in hematologic malignancies. Indeed, an early study demonstrated that the incidence of FN mortality was as high as over 10 % in some hematological malignancies which was obviously higher than that observed in solid cancers. Thus, patients with hematologic malignancies are potentially at higher risk for death due to infection[1,2]. In addition, infections also frequently occur in the absence of neutropenia in hematologic disorders due to the disease-oriented latent severe immune impairment of the patients[3].

BSI, bacteremia and septicemia, is one of the most frequent and life-threatening systemic infections. The prognosis of patients with proven BSI is poorer compared with that of patients without pathogen detection, and the mortality rate has been associated with the type of pathogen in patients with proven bacteremia. Therefore, adequate microorganism detection by Blood Culture (BC) tests along with early intervention involving empiric antibiotic therapy are critically important in hematologic malignancies when febrile events occur. It has been noted that up to three or four BC tests are needed for achieving > 99 % test sensitivity for detection of the causative bacteria[4,5]. However, the incidence of positive microbiological detection by BC tests has been low. Importantly, the spectrum of pathogens detected by the BC test has changed with the time depending on various factors, such as types of prophylactic agents, the usage of either a Central Venous Catheter (CVC) or external lines, BSI recurrence, and types of treatment for the primary hematologic diseases[6-8]. Indeed, the most prevalent causative microorganisms were Gram-negative species, such as *Pseudomonas aeruginosa* or *Escherichia coli*, from the 1970's to the late 1980's. During the last two decades, the types of microorganisms found associated with hematologic malignancies have generally tended to shift to Gram-positive organisms, such as *Enterococcus species* or *Staphylococcus* species[4,5,9]. However, even this trend has not been always the case in recent studies[10], and, more importantly, the increase in drug resistant microorganisms, such as methicillin resistant, Extended-Spectrum Beta-Lactamase (ESBL) producing, carbapenemase producing, and vancomycin resistant bacteria, as the causative pathogen for BSI has become an emerging problem in the hematology/oncology field[11,12]. In this study, we conducted a retrospective analysis involving a 5-year surveillance of BC tests obtained from febrile patients with hematological disorders to update the current status of BSI in hematologic diseases. We also investigated the relationship between infection by drug resistant bacteria and disease/treatment factors, such as neutropenia, the use of prophylactic fluoroquinolones (FQs), and the use of a CVC.

Materials and methods

Patients and BC assessment for microbes

This study included BC samples from febrile hospitalized patients with hematologic disorders during the time period of January 2010 through December 2014 at the Division of Hematology and Oncology, Kyoto Prefectural University of Medicine. The use of prophylactic antibiotics, including FQs (mainly Levofloxacin), Sulfamethoxazole/Trimetoprim (ST), and antifungal azoles, was determined by the physicians. Two sets of blood samples were generally obtained from febrile patients with an axillary temperature above 37.6°C. The first BC test was performed before initiation of the therapeutic antibiotics, while the later BC tests were performed at fever elevation despite the treatment with broad spectrum antibiotics, including either Cefepime Hydrochloride (CFPM), Tazobactam/ Piperacillin (TAZ/PIPC),or Meropenem Hydrate (in cases of adverse events with CFPM and/or TAZ/PIPC). In patients with a CVC, one of the BC samples was obtained through the central catheter and the other from a peripheral venipuncture site. In patients without a CVC, two sets of BC samples were obtained from two different peripheral venipuncture sites. An automated microbial detection system (BacT/ALERT 3D; bioMérieux, Marcy l'Etoile, France) was used for bacterial culture for 5 days. Microorganism identification and antibiotic susceptibility testing were performed using VITEK2 (bioMérieux). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the institutional review boards.

Statistical analyses

All calculations were performed with Microsoft Excel 2010 (Microsoft, Redmond, WA). The chi-square test was used for quantitative comparison of variables between two groups. All P values were two-sided, and P values < .05 were considered to be statistically significant.

Results

Backgrounds of patients

During the observation period, a cumulative number of 8,549 BC tests from 1,517 febrile events with 388 patients (normally two BC tests were performed with one fever elevation, unless venous puncture was inaccessible), were retrospectively analyzed. Among them, 325 BC tests (3.8 %) showed positive results in 154 febrile episodes (10.1 %) with 91 patients, including 49 patients (53.8 %) with non-Hodgkin lymphomas and 21 (23.1 %) with leukemias, and a total of 164 microorganisms were identified as causative pathogens. The median age of the 91 patients was 66 (17 - 92), and 52.7 % were male. Eleven and 15 patients were shown positive BC tests after autologous and allogeneic Hematopoietic Stem Cell Transplantation (HSCT), respectively (Table 1). Of 91 positive BC patients, FQs were used for prophylaxis in 81 patients (89.0 %) and ST for prophylaxis against Pneumocystis jiroveci pneumonia in 77 patients (84.6 %). Antifungal prophylaxes were given in 70 patients (76.9 %), with fluconazole in 38(41.8 %), itraconazole in 19 (20.9 %), micafungin in 6(6.6 %), voriconazole in 5(5.5 %) and liposomal amphotericin B in 2(2.2 %).

Table 1: Patient's Background.

	Patients with positive BC (n=91)	%
Age, median (range)	66 (17-92)	
Male/Female	48/43	52.7/47.3
Disease		
AML	15	16.5
ALL	3	3.3
CML	3	3.3
MDS	5	5.5
NHL	49	53.8
DLBCL	24	26.4
FL	7	7.7
HL	1	1.1
MM	9	9.9
Other benign disorders (AA, ITP, neutropenia by other causes)	6	6.6
Autologous HSCT	11	
Allogeneic HSCT	15	

Cumulative numbers and ratios of patients with positive BC tests are shown, AML: Acute Myelogenous Leukemia, ALL: Acute Lymphoblastic Leukemia, CML: Chronic Myelogenous Leukemia, MDS: Myelodysplastic Syndromes, NHL: Non-Hodgkin Lymphomas, DLBCL: Diffuse Large B-Cell Lymphoma, FL: Follicular Lymphoma, HL: Hodgkin lymphoma, MM: Multiple Myeloma, AA: Aplastic Anemia, ITP: Immune Thrombocytopenic Purpura, HSCT: Hematopoietic Stem Cell Transplantation.

Table 2: Microorganisms detected by BC tests.

	Number	%
Gram positive cocci	73	44.5
MRSE	35	21.3
Streptococcus spp.	12	7.3
MRCNS	11	6.7
Enterococcus faecalis	5	3.0
MSSA	1	0.6
MRSA	1	0.6
Staphylococcus epidermidis	1	0.6
others	9	
Gram negative rods	71	43.3
Escherichia coli (ESBL)	42	25.6
Escherichia coli (non-ESBL)	13	7.9
Pseudomonas aeruginosa	4	2.4
Enterobacter spp.	2	1.2
Klebsiella pneumoniae (ESBL)	2	1.2
Klebsiella pneumoniae (non-ESBL)	2	1.2
others	7	4.3
Anaerobic bacteria	2	1.2
non-*Bacteroides spp.*	2	1.2
Fungus	3	1.8
Candida spp.	3	1.8
Others	15	
total	164	

The list of causative pathogens
ESBL: Extended-Spectrum Beta-Lactamase, MRSE: Methicillin-Resistant *Staphylococcus epidermidis*, MRCNS: Methicillin-Resistantcoagulase Negative *Staphylococci*, MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: Methicillin-Resistant *Staphylococcus aureus*

Profiles of microorganisms detected by the BC tests

In total, 164 microorganisms were identified as causative pathogens (Table 2). One pathogen was detected by two independent BC tests in one febrile event with most patients, while sometimes the pathogen was detected in more than three independent BC tests, including 7 BC tests in one patient with a methicillin-susceptible *Staphylococcus aureus* infection. More than two different microorganisms were detected by one BC test for one febrile event in 10 patients. In a limited number of patients, a single positive test was considered to indicate the presence of a pathogen based on additional clinical criteria, such as the lack of a later BC test due to the quick resolution of symptoms with antibiotic therapy. In these BC-positive episodes, 88.3 % (136/154) were detected in the first BC test, 95.5 % (147/154) were detected by up to the second BC test, 98.1 % (151/154) were detected by up to the third BC test, and 3 of 154 were detected in the 4 - 5th BC tests (Table 3). Overall, the ESBL producing *Escherichia coli (E.coli*) was the most frequently detected pathogen, accounting for 25.6 % of all positive BC tests, and Methicillin-Resistant *Staphylococcus Epidermidis* (MRSE) was the second most frequently detected pathogen, accounting for 21.3% of all positive tests. The incidences of Methicillin-Resistant coagulase Negative *Staphylococci* (MRCNS), *Streptococcus* species, and non-ESBL *E.coli* were similar, each accounting for approximately 6 - 8 % of all positive BC tests (Table 2). Neither carbapenemase-producing bacteria nor vancomycin resistant bacteria were detected in our cohort. The recurrent rate of the same pathogens in the same patient was 26.4 % (24 of 91 patients), meanwhile those of MRSE/MRCNS and ESBL producing bacteria were 27.3 % (9 of 33 patients) and 47.8 % (11 of 23 patients), respectively.

Table 3: The number of BC tests and the detection of microorganisms.

	1st	2nd	3rd	4th	5th
E-coli					
All	47	4	1	0	0
(ESBL)	(38)	(3)	(1)	(0)	(0)
MRSE	30	1	1	2	1
Streptococcus spp.	12	0	0	0	0
MRCNS	10	1	0	0	0
Enterococcus faecium	5	1	3	0	0
Enterococcus faecalis	4	1	0	0	0
Pseudomonas aeruginosa	4	0	0	0	0
Klebsiella Pneumoniae					
All	3	1	0	0	0
(ESBL)	(1)	(1)	(0)	(0)	(0)
Bacillus spp.	2	0	0	0	0
MSSA	1	0	0	0	0
MRSA	1	0	0	0	0
others	26	2	0	0	0
overlap	9	0	1	0	0
total	145	11	5	2	1

Clinical characteristics of BSI by drug-resistant microorganisms

Given the high frequency of drug-resistance microor-

ganisms, we investigated whether neutropenia and critical treatment components were associated with a positive BC test with the emergence of BSI by either ESBL-producing *E.Coli* or methicillin-resistant *Staphylococci*. As shown in Table 4, the use of a CVC positively associated with emergence of methicillin-resistant *Staphylococci* BSI and negatively associated with infection by ESBL-producing Gram-negative bacteria-induced BSI in our cohort (P = 0.002). In contrast, FN and the prophylactic use of FQs did not associate with BSI by either ESBL-producing bacteria or methicillin-resistant *Staphylococci*. In our cohort, the use of a CVC significantly associated with younger age (median: 62 years old, range 18 - 82 *vs*. 70, range 18 - 79, P < 0.001) because of higher rates of indication for intensive chemotherapy, while the incidence of positivity at first BC test (88.0 % *vs*. 92.6 %, P = 0.201) was not associated with CVC [CVC(+) vs. CVC(-), 88.0% *vs*. 92.6 % , P = 0.373].

Table 4: Association between the detection of drug-resistant bacteria and the patient's condition.

		ESBL +ve (n=44)	MRSE/MRCNS +ve (n=44)	Others (n=66)	P-value
CVC+	(n=100)	22	37	41	0.002
CVC-	(n=54)	22	7	25	
neutropenic	(n=73)	16	22	35	0.211
non-neutropenic	(n=81)	28	22	31	
FQ+	(n=81)	28	25	28	0.074
FQ-	(n=73)	16	19	38	

CVC: Central Venous Catheter, FQ: Fluoroquinolone

Discussion

The spectrum of microorganisms detected by the BC test is strongly influenced by various clinical factors, such as the patients' condition, underlying diseases, and the use of prophylactic antibiotics, and has changed with the time. In our cohort treated from 2010 to 2014, the frequencies of Gram-positive and Gram-negative bacteria as the pathogen were almost equal. This result is intermediate between two previous studies; one emphasizes the high frequency of Gram-positive bacteria as the causative pathogen in the recent era[4,5,9] and the other identified Gram-negative species as more frequent causative pathogen[10]. In addition, our results differ from a previous study in that fungi were detected as a pathogen only in 1.8 % of the events[4]. However, one should carefully monitor additional serological/radiological tests for fungal infection, as the bacterial culture test is not sufficiently sensitive for the early diagnosis of fungal infection[13]. These findings collectively suggest the importance of the empiric use of broad spectrum antibiotics which cover both Gram-positive and negative bacteria, while the therapeutic use of antifungal agents should evaluated by careful observations.

The most serious issue in this study was the high incidence of drug resistant microorganisms, especially MRSE, MRCNS, and ESBL-producing gram-negative bacteria, accounting for approximately 60 % of the bacterial pathogens for the last three years. The frequencies of MRSE/MRCNS and ESBL-producing bacteria in this study were obviously higher than those from all the departments in our hospital, approximately 16.8 % for MRSE/MRCNS and 5.2 % for ESBL-producing bacteria. These results suggest that the frequency of the resistant pathogens associated with hematologic diseases is probably higher than that of nosocomial infections in our hospital. Although we did not find a statistically significant association between the use of prophylactic FQ or neutropenia and the detection of drug resistant bacteria in our cohort, there was a weak trend for a higher frequency of ESBL-producing bacteria in patients with prophylactic FQ conceivably suggesting the possible relationship of ESBL production with FQ resistance. Although prophylactic FQ reduces the overall risk of FN[14], further study is needed to address whether the prophylactic use of FQ potentially induces the emergence of ESBL-producing bacteria-derived infections in a clinical setting[15]. The other important aspect of our result on drug resistant bacteria was their association with the use of a CVC. In our cohort, the use of a CVC negatively associated with the detection of ESBL-producing bacteria, and positively associated with that of methicillin-resistant bacteria. A CVC is normally utilized for patients receiving aggressive treatments, including either chemotherapy, HSCT, or powerful immunosuppressive therapies, such as either anti-thymocyte globulin or intravenous treatment with a calcineurin inhibitor. Thus, rigorous preventive care against methicillin-resistance bacteria is still recommended during the use of a CVC in patients with hematologic diseases experiencing long-term hospitalization[16]. In contrast, ESBL-producing bacteria were not associated with the use of a CVC, but were frequently detected even at the first febrile event. Conceivably, this might reflect the increase of ESBL-producing bacteria carriers in the community[17]. While empiric treatment using either carbapenems or glycopeptides as the initial approach for FN is not recommended in patients without particular risk factors to avoid the emergence of the resistant bacteria against those agents[18], our results support the notion that targeting drug resistant bacteria should be initiated, once the conventional empiric therapy with either CFPM or TAZ/PIPC is not effective and a patient has deteriorated in a few days[18].

Although the BC test is the cornerstone for the diagnosis and treatment of BSI, its accuracy has not been sufficiently high. As found in our study, the positive detection accuracy of BCs in hematological disorders has been reported to be low, about 10% in FN patients and around 10 - 20 % even in patients with common and expected infections[19] Our results revealed that the incidence of BC-positivity by up to the 3rd BC tests was 98.1 % in BC-positive febrile episodes, and this result was similar with that of previous studies[4,5]. Considering the highly enhanced positive detection with the three BC tests in the BC-positive patients despite the overall low positive detection rates, antibiotic therapy should be used in the absence of detected microorganism in most cases, when the first three BC tests fail to detect a pathogen. Thus, our results may be instructive for

the selection of antibiotics, especially, alerting physicians to the high frequency of drug resistant microorganisms associated with specific treatments and patient conditions[20].

In conclusion, our study found increasing frequencies of drug-resistant bacteria as the pathogens of BSI in hematological disorders even in the first febrile episode. Our study provides information for the selection of the first and, in the cases where necessary, second-line empiric antibiotic therapies.

Conflict of Interest: The authors declare no potential conflicts of interest.

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