Journal of Microbiology, Immunology and Infection (2018) 51, 123–131

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Characteristics comparisons of bacteremia in allogeneic and autologous hematopoietic stem cell-transplant recipients with levofloxacin prophylaxis and influence on resistant bacteria emergence

Ching-Hsun Wang [a], Feng-Yee Chang [a], Tsu-Yi Chao [b], Woei-Yau Kao [c], Ching-Liang Ho [d], Yeu-Chin Chen [d], Ming-Shen Dai [d], Ping-Ying Chang [d], Yi-Ying Wu [d], Jung-Chung Lin [a,*]

[a] *Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[b] *Department of Hematology Oncology, Taipei Medical University — Shuang Ho Hospital, Ministry of Health and Welfare, Taipei, Taiwan*
[c] *Division of Hematology Oncology, Department of Internal Medicine, Taipei Tzu Chi General Hospital, Taipei, Taiwan*
[d] *Division of Hematology Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*

Received 7 September 2015; received in revised form 18 December 2015; accepted 24 February 2016
Available online 17 March 2016

KEYWORDS
bacteremia;
levofloxacin;
prophylaxis;
transplantation

Abstract *Background:* The aim of this study was to compare the risk factors and clinical outcomes of bacteremia in allogeneic and autologous hematopoietic stem cell transplant (allo-HSCT and auto-HSCT) recipients with levofloxacin prophylaxis during the early period after transplantation.
Methods: Characteristics of bacteremia within 45 days after transplantation between allo-HSCT and auto-HSCT recipients who received levofloxacin prophylaxis between January 2005 and December 2014 were retrospectively reviewed.
Results: Of 105 HSCT recipients included in this study, 55 (52.4%) received an allo-HSCT and 50 (47.6%) received an auto-HSCT. Twenty-five patients (23.8%) with HSCT developed 28 episodes of bacteremia. Of these 25 bacteremia patients, 15 received an allo-HSCT, while 10 received an

* Corresponding author. Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Number 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan.
E-mail address: linjungchung1@yahoo.com.tw (J.-C. Lin).

http://dx.doi.org/10.1016/j.jmii.2016.02.003

auto-HSCT. The occurrence of Grade 3–4 graft-versus-host disease and longer engraftment duration were associated with bacteremia in allo- and auto-HSCT recipients ($p = 0.001$ and $p = 0.002$, respectively). Auto-HSCT recipients with bacteremia had a longer hospital stay after transplantation, while allo-HSCT recipients with bacteremia had an increased 45-day mortality rate as compared with those without bacteremia ($p = 0.014$ and $p = 0.013$, respectively). All 14 Gram-negative blood isolates in this study were resistant to fluoroquinolone.

Conclusion: Levofloxacin prophylaxis in HSCT recipients is associated with the emergence of fluoroquinolone-resistant Gram-negative bacteria. The risk factors and clinical outcomes of bacteremia differ between allo- and auto-HSCT recipients, and these differences should be taken into account when designing strategies to prevent bacteremia.

Introduction

Bacteremia is a common infectious complication in patients undergoing hematopoietic stem cell transplantation (HSCT), with an incidence that ranges from 18.6% to 43.6%, depending on study design, population, and transplantation protocol used.[1–5] When bacteremia occurs in HSCT recipients, it is associated with increased morbidity and mortality.[4,6–8] Based on evidence that antibiotic prophylaxis improves clinical outcomes in patients with neutropenia after chemotherapy, the use of prophylactic antibiotics was recommended for allogeneic and autologous HSCT (allo-HSCT and auto-HSCT) recipients.[9,10] A recent meta-analysis of HSCT recipients showed that primary prophylaxis with antibiotics reduced the incidence of bacteremia as compared with no prophylaxis.[11] Despite the clinical benefits of primary antibiotic prophylaxis in HSCT recipients, concerns remain over the possible increase in antibiotic resistance.[12–15]

In Taiwan, most centers used fluoroquinolone for bacterial prophylaxis in HSCT recipients as recommended. Previous studies on the experience of fluoroquinolone prophylaxis in HSCT recipients in Taiwan focused mostly on allo-HSCT recipients.[16–18] Information concerning fluoroquinolone prophylaxis in auto-HSCT recipients has not yet been reported. Our institution has used levofloxacin for primary bacterial prophylaxis during the neutropenic phase in auto-HSCT and allo-HSCT recipients since January 2003. Initially, we used a dose of 500 mg/day; however, based on evidence that a higher dose of levofloxacin (750 mg/day) exhibited better antibacterial activity against *Pseudomonas* spp. and similar tolerance rates as compared with a lower dose of levofloxacin (500 mg/day), we shifted to a higher dose of levofloxacin (750 mg/day) in January 2011.[19]

The purpose of this study was to compare the risk factors and clinical outcomes of patients with bacteremia according to the type of HSCT received and following levofloxacin prophylaxis after transplantation and analyze resistant patterns of blood isolates.

Methods

Study design

A retrospective chart review was conducted at the Tri-Service General Hospital, National Defense Medical Center, which is a 1700-bed teaching hospital in Taiwan. Patients ≥18 years of age that had received an allo-HSCT or auto-HSCT between January 2005 and December 2014, and had received levofloxacin for primary bacterial prophylaxis during the peritransplantation period, were included in this study. Patients who had received more than one HSCT were treated as multiple patients for the purpose of this study. The clinical characteristics, outcomes, and microbiological data of blood isolates from patients were retrieved by reviewing their medical charts. This study was approved by the Institutional Review Board of the hospital (TSGHIRB approval number: 1-103-05-015).

Transplantation environment and supportive care

All patients receiving a transplant stayed in the transplantation unit of the hospital, which consists of a specialized single room with the standard protective environment. The transplantation unit was equipped with high-efficiency particulate air filters and reverse-osmosis water systems for a clean water supply. Other protective measures in the unit included standard precautions for healthcare workers and low microbial-content diets.

The patients were implanted with a Hickman catheter before initiating the conditioning regimen for drug infusion and parental nutrition. Granulocyte colony-stimulating factor was transfused from the day of transplant until engraftment. Patients were advised to gargle with a 0.2% chlorhexidine gluconate solution twice a day from the start of conditioning chemotherapy for oral hygiene and to continue until the mucositis was resolved. The transplantation protocol for each patient was reviewed and approved by the cancer committee in our institution before the transplant.

Infection prophylaxis and management

All patients received acyclovir for antiviral prophylaxis from the start of conditioning until engraftment. Auto-HSCT recipients received oral fluconazole tablets, while allo-HSCT recipients received oral fluconazole tablets (from January 2005 to June 2011) or an oral suspension of posaconazole (from July 2011 to Dec 2014) for antifungal prophylaxis. Both allo-HSCT and auto-HSCT recipients were given oral levofloxacin for bacterial prophylaxis, at a dose of 500 mg/day from January 2005 to December 2010, and

750 mg/day from January 2011 to December 2014. The duration of antifungal and antibacterial prophylaxis in allo- and auto-HSCT recipients was the same as that used for the antiviral prophylaxis.

Neutropenic fever was defined as an oral temperature $>38.3^{\circ}C$ and an absolute neutrophil count $<500/\mu L$. When febrile neutropenia occurred in patients, chest radiography was performed, and urine, sputum, and blood were sent for culture. High-resolution computed tomography (CT) of the thorax was performed if the chest X-ray findings or clinical presentations were suggestive of an invasive fungal infection. Abdominal sonography or CT was performed if clinical symptoms and signs were suggestive of an abdominal infection. The initial prophylactic antibiotics were discontinued, and broad spectrum antibiotics were given empirically after a thorough assessment by an infectious-disease specialist in accordance with guidelines of the Infectious Diseases Society of America and Taiwan.[20,21] A parenteral broad-spectrum antifungal agent was also administered empirically if clinical characteristics suggested an invasive fungal infection in febrile patients after being assessed by two different infectious-disease specialists and a hematologist. Tests for galactomannan and (1−3)-β-D-glucan were not available during the study period.

Definitions and data collection

Early infections recorded in our study were defined as infection episodes occurring during the pre-engraftment risk period defined as 45 days after transplantation.[22] Early mortality was defined as death within 45 days after transplantation. Cause of death was recorded according to the coding on the medical records as primary cause of death. Infection episodes occurring during this period and related clinical information in patients were retrieved via medical chart review. Engraftment was defined as an absolute neutrophil count $>500/\mu L$ after the nadir absolute count. Bacteremia was defined as a recognized pathogen cultured from one or more blood cultures, or cultured from two or more blood cultures drawn on separate occasions, with signs of sepsis if a common skin contaminant (i.e., diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci, viridians group streptococci, *Aerococcus* spp., or *Micrococcus* spp.) was identified. Infections other than bacteremia were recorded according to Centers for Disease Control definition of health care-associated infections.[23] Invasive fungal infections were classified as possible, probable, or proven, based on the 2008 criteria of the European Organization for Research and Treatment of Cancer.[24] Cytomegalovirus (CMV) end-organ disease was defined as the isolation of CMV or detection of viral proteins or nucleic acids in tissue specimens, along with associated symptoms and signs.[25] Blood isolates were not preserved in our hospital; therefore, we retrospectively reviewed positive blood-culture reports and reassessed antibiotic sensitivity according to the Clinical Laboratory Standards Institute 2013 criteria.[26] In this study, ciprofloxacin sensitivity was used as an indicator of fluoroquinolone sensitivity in Gram-negative bacteria, and levofloxacin and moxifloxacin sensitivity was used as an indicator of fluoroquinolone sensitivity in *Streptococcus* spp. and *Staphylococcus* spp., respectively. Multiple-drug resistance in Gram-negative bacteria was defined as resistance to more than three classes of antibiotics.[27]

Statistical analysis

Data were stratified on the basis of HSCT type and presence or absence of bacteremia. Data were compared between allo- and auto-HSCT recipients using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed with the Chi-square or Fisher's exact test, as appropriate, and continuous variables were analyzed with the Mann-Whitney U test. All p-values were 2-tailed, and a $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

During the study period, 111 patients underwent HSCT at our institution. Three patients <18 years of age were excluded, and another three patients were excluded, because they did not receive levofloxacin for bacterial prophylaxis. Therefore, a total of 105 patients were included in this analysis. Of these 105 patients, 55 underwent allo-HSCT and 50 underwent auto-HSCT.

The median age of allo-HSCT recipients was less than auto-HSCT recipients (30 years vs. 42 years, $p < 0.001$). The most common hematological disease in allo- HSCT and auto-HSCT recipients was acute myeloid leukemia and lymphoma. Among patients receiving auto-HSCT recipients with lymphoma and leukemia ($n = 35$), 19 (54.3%) were in complete remission at transplant. In allo-HSCT recipients with leukemia and lymphoma ($n = 42$), 18 (42.8%) were in complete remission. The median cycles of chemotherapy within 6 months before transplantation in allo- HSCT and auto-HSCT recipients were 3 (range: 0−6) and 2.5 (range: 0−16), respectively. The duration of engraftment was longer in allo-HSCT recipients as compared with auto-HSCT recipients (17 days vs. 12 days, $p < 0.001$). Allo-HSCT recipients had a higher early mortality rate (12.7% vs. 4.0%, $p = 0.165$) relative to auto-HSCT recipients, but significance for this finding was not observed.

Early infectious complications in allo- and auto-HSCT recipients

One hundred and seventeen infectious episodes occurred in 95 recipients during the early-risk period, with 69 and 48 episodes in allo- and auto-HSCT recipients, respectively. The most frequent diagnosis was fever of unknown origin ($n = 47$, 40.2%), followed by bacteremia ($n = 28$, 23.9%) and lower respiratory tract infection ($n = 25$, 21.4%). Other infections included oral cavity infection ($n = 6$, 5.2%), soft-tissue infection ($n = 4$, 3.5%), urinary tract infection ($n = 2$, 1.6%), and gastrointestinal tract infection ($n = 1$, 0.8%). Additionally, two invasive fungal infections and two CMV end-organ diseases were also noted. Among patients with infection ($n = 95$), 11/95 (11.5%) patients suffered

from septic shock when infection occurred. Early mortality in allo- and auto—HSCT recipients was 12.7% and 4%, respectively. Among allo-HSCT recipients who died in the early period ($n = 7$), five deaths were attributed to bacteremia, one to lower respiratory tract infection, and one pulmonary hemorrhage. Among early mortality cases in auto-HSCT recipients ($n = 2$), one died of bacteremia and the other of lower respiratory tract infection.

Table 1 Transplantation characteristics and outcomes of patients receiving HSCT with bacteremia.

Outcome	Characteristic							
	Allo-HSCT ($n = 55$)				Auto-HSCT ($n = 50$)			
	Bacteremia	No bacteremia	p[a]	All	Bacteremia	No bacteremia	p[a]	All
Number of patients, *n* (%)	15 (27.2)	40 (72.8)		55 (100.0)	10 (20.0)	40 (80.0)		50 (100.0)
Age, y [b]	30 (18—60)	30.5 (18—62)	0.798	30 (18—62)	38 (21—67)	44 (18—63)	0.752	42 (18—67)
Male gender, *n* (%)	9 (60.0)	30 (75.0)	0.326	39 (70.9)	6 (60.0)	23 (57.5)	>0.99	28 (56.0)
Primary diagnosis, *n* (%)								
Lymphoma	0 (0.0)	3 (7.5)		3 (5.4)	8 (80.0)	23 (57.5)		31 (62.0)
Aplastic anemia	2 (13.3)	5 (12.5)		7 (12.7)	0 (0.0)	0 (0.0)		0 (0.0)
Acute myeloid leukemia	5 (33.3)	15 (37.5)		20 (36.3)	0 (0.0)	4 (10.0)		4 (8.0)
Acute lymphoblastic leukemia	7 (46.6)	12 (30.0)		19 (34.5)	0 (0.0)	0 (0.0)		0 (0.0)
Myelodysplastic syndrome	1 (6.6)	2 (5.00)		3 (5.4)	0 (0.0)	0 (0.0)		0 (0.0)
Chronic myeloid leukemia	0 (0.0)	3 (7.5)		3 (5.4)	0 (0.0)	0 (0.0)		0 (0.0)
Multiple myeloma	0 (0.0)	0 (0.0)		0 (0.0)	2 (20.0)	13 (32.5)		15 (30.0)
Donor type, *n* (%)								
MUD	5 (33.3)	19 (47.5)		24 (43.6)				
MMUD	2 (13.3)	4 (10.0)		6 (10.9)				
MFD	8 (53.3)	17 (42.5)		25 (45.4)				
Stem cell source, *n* (%)								
Peripheral blood	15 (100.0)	38 (95.0)	>0.99	53 (96.4)				
Umbilical cord blood	0 (0.0)	2 (5.0)		2 (3.6)				
Total body irradiation, *n* (%)	3 (20)	15 (38.5)	0.197	18 (32.7)				
Condition regimen, *n* (%)								
Myeloablative	10 (66.7)	28 (70.0)	>0.99	38 (69.0)	10 (100.0)	40 (100.0)		50 (100.0)
Reduced intensity	5 (33.3)	12 (30.0)		17 (30.9)	0 (0.0)	0 (0.0)		0 (0.0)
GVHD prophylaxis, *n* (%)								
Methotrexate + cyclosporine	9 (60.0)	19 (47.5)	0.409	28 (50.9)				
Methotrexate + cyclosporine + ATG	6 (40.0)	21 (52.5)		27 (49.1)				
Acute GVHD, *n* (%)								
Grade 3—4	6 (40.0)	1 (2.5)	0.001	7 (12.7)				
Grade 0—2	9 (60.0)	39 (97.5)		48 (87.2)				
Engraftment duration [b]	18 (12—31)	17 (13—29)	0.494	17 (12—31)	15 (11—20)	12 (9—26)	0.002	12 (9—26)
High dose levofloxacin prophylaxis, *n* (%)	6 (40.0)	15 (37.5)	>0.99	21 (38.1)	4 (40.0)	21 (52.5.)	0.725	25 (50.0)
Early mortality, *n* (%)	5 (33.3)	2 (5.0)	0.013	7 (12.7)	1 (10.0)	1 (2.5)	0.363	2 (4.0)
Hospital stay after HSCT in survivals[b]	39 (20—94)	32 (22—101)	0.257	33 (20—101)	25 (20—50)	21 (12—74)	0.014	23 (12—74)

[a] For comparison of the patients with and without bacteremia in allo-HSCT and auto-HSCT groups, respectively.
[b] Data are presented as medians (range).
Allo-HSCT = allogeneic hematopoietic stem cell transplantation; ATG = antithymocyte globulin; Auto-HSCT = autologous hematopoietic stem cell transplantation; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; MFD = mismatched family donor; MMUD = mismatched unrelated donor; MUD = matched unrelated donor.

Table 2 Blood isolates from HSCT recipients and their antibiotic resistance patterns.

Gram-positive organism, *n* (%)	No.	Pen	Amp	Ox	Van	Tei	Ery	CC	FQ
Streptococcus spp.	4	2 (50.0)			0 (0.0)		3 (75.0)	2 (50.0)	2 (50.0)
Coagulase-negative *staphylococcus*	5	4 (80.0)		2 (40.0)	0 (0.0)	0 (0.0)	3 (60.0)	1 (20.0)	2 (40.0)
Rothia spp.	1	0 (0.0)							
Staphylococcus aureus	1	1 (100.0)		1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)
Staphylococcus saprophyticus	1	0 (0.0)		1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)
Enterococcus feceium	1		1 (100.0)		1 (100.0)				

Gram-negative organism, *n* (%)	No.	Amp	CF	GM	CAZ	AMS	TZP	CRO	IMP	FQ	FEP	MDR
Escherichia coli	7	7 (100.0)	3 (42.8)	4 (57.1)	1 (14.2)	6 (85.7)	0 (0.0)	1 (14.2)	0 (0.0)	7 (100.0)	1 (14.2)	6 (85.7)
Klebsiella pneumonia	2	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	0 (0.0)	2 (100.0)	2 (100.0)	2 (100.0)
Serratia marcescens	1	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)
Achromobacter xylosoxidans	1	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)			1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)
Acinetobacter baumannii	1	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
Enterobacter cloacae	1	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)
Acinetobacter lwoffii	1	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)

Anaerobic bacteremia, *n* (%)	No.	Pen	CC	AMS	TZP	METR
Bacteroides thetaiotaomicron	1	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)

Amp = ampicillin; AMS = ampicillin-sulbactam; CAZ = ceftazidime; CC = clindamycin; CF = cefazolin; CRO = ceftriaxone; Ery = erythromycin; FEP = cefepime; FQ = fluoroquinolone; GM = gentamycin; HSCT = hematopoietic stem cell transplantation; IMP = imipenum-cilastatin; MDR = multiple-drug resistance; METR = metronidazole; Ox = oxacillin; Pen = penicillin; Tei = teicoplanin; TZP = piperacillin-tazobactam; Van = vancomycin.

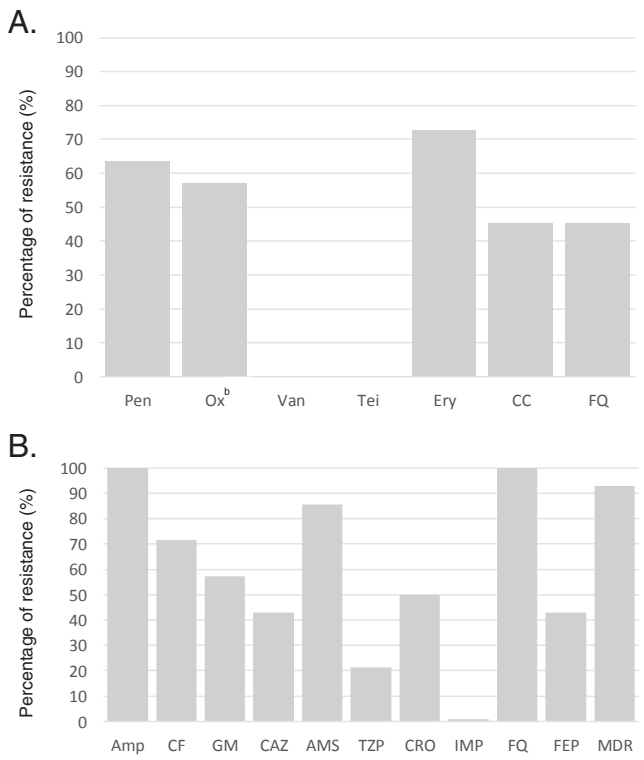

Figure 1. *In vitro* antibiotic resistance rate of (A) Gram-positive [a] and (B) Gram-negative blood isolates from hematopoietic stem cell transplantation recipients. [a] *Enterococcus* and *Rothia* spp. were excluded for analysis. [b] Only *staphylococcus* spp. was tested. Amp = ampicillin; AMS = ampicillin-sulbactam; CAZ = ceftazidime; CC = clindamycin; CF = cefazolin; CRO = ceftriaxone; Ery = erythromycin; FEP = cefepime; FQ = fluoroquinolone; GM = gentamycin; IMP = imipenum-cilastatin; MDR = multiple-drug resistance; Ox = oxacillin; Pen = penicillin; Tei = teicoplanin; TZP = piperacillin-tazobactam; Van = vancomycin.

Bacteremia in allo- and auto—HSCT recipients

Table 1 summarizes the clinical characteristics of allo- and auto—HSCT recipients with and without bacteremia. Eighteen episodes of bacteremia occurred in 16 allo-HSCT recipients, while 10 episodes occurred in 10 auto-HSCT recipients. There were no episodes of post-neutrophil-engraftment bacteremia in auto-HSCT recipients, while two of the 55 allo-HSCT recipients (3.6%) experienced post-neutrophil-engraftment bacteremia and had concomitant Grade 3—4 acute graft-versus-host disease (GVHD). The median bacteremia onset duration was 9.5 (range: 0—40) and 9 (range: 4—11) days in allo-HSCT recipients and auto-HSCT recipients, respectively, after transplantation. Among allo-HSCT recipients with bacteremia ($n = 15$), six (40%) suffered from septic shock from bacteremia, with 33.3% early mortality. In auto-HSCT recipients with bacteremia ($n = 10$), septic shock occurred in one patient (10%) at bacteremia onset, with 10.0% early mortality.

Grade 3—4 GVHD in allo-HSCT recipients was associated with bacteremia (40.0% vs. 2.5%, $p = 0.001$), and longer engraftment duration after transplantation was associated with bacteremia in auto-HSCT recipients ($p = 0.002$). Bacterial prophylaxis using a higher dose of levofloxacin (750 mg/day) had no influence on the incidence of bacteremia as compared with the lower dose (500 mg/day) in allo- and auto-HSCT recipients ($p > 0.99$ and $p = 0.725$, respectively). Patients with bacteremia exhibited higher early mortality relative to those without bacteremia (33.3% vs. 12.5%, $p = 0.013$). Auto-HSCT recipients with bacteremia showed no difference in mortality ($p = 0.363$), but had a longer hospital stay after transplantation as compared with patients without bacteremia (25 days vs. 21 days, $p = 0.014$).

Blood isolates from HSCT recipients

Blood isolates from HSCT recipients and related antibiograms are summarized in Table 2 and Figure 1. Of the 28 bacterial isolates, 13 were Gram-positive, 14 were Gram-negative, and one was anaerobic. The most common Gram-positive blood isolates were coagulase-negative *Staphylococci*, while *Escherichia coli* was the most commonly isolated Gram-negative bacteria. All Gram-negative bacteria were resistant to fluoroquinolone, and most Gram-negative bacteria (92.8%) were also multiple-drug resistant.

Discussion

Our study revealed that bacteremia accounted for the majority of early mortality in HSCT recipients after transplantation. The risk factors and clinical outcomes of bacteremia between allo- and auto-HSCT recipients were different, despite receiving identical supportive care and prophylactic antibiotics. Additionally, we observed emergence of fluoroquinolone-resistant and multiple-drug resistant Gram-negative bacteria in both allo- and auto-HSCT recipients after levofloxacin use.

In auto-HSCT recipients, longer durations of neutropenia were associated with the occurrence of bacteremia. This result was consistent with results from previous studies.[7,28,29] Reducing the duration of neutropenia may, therefore, help decrease the incidence of bacteremia. Peripheral-blood stem cell transplants and use of growth factors in auto-HSCT recipients were reported to shorten the duration of neutropenia and were routinely used in our transplantation protocol.[29,30]

Previous reports showed that the severity of mucositis was associated with bacteremia and reduced survival.[31,32] Current oral hygiene measures in our protocols included daily gargling with a chlorhexidine gluconate solution only during the peritransplantation period. Recently, a new agent, palifermins, which is a keratinocyte growth factor, was approved by the Food and Drug Administration to reduce the severity of mucositis in auto-HSCT recipients after chemotherapy. However, its clinical efficacy in improving infectious complications and overall survival remain uncertain.[33,34] The use of this new agent in HSCT recipients may be another way to decrease bacteremia and improve outcomes.

In allo-HSCT recipients, acute GVHD Grade 3—4 was associated with bacteremia, but the relationship was

complex. Acute GVHD may explain the post-engraftment bacteremia: bacteria traversed the breaks in mucosa of the oral cavity and gastrointestinal tract, resulting in bacteremia.[35,36] Most cases of bacteremia in our study, however, occurred during the neutropenic phase when GVHD had not yet occurred. A possible explanation is that cytokines released during bacteremia in the pre-engraftment period precipitated the subsequent occurrence of GVHD.[37,38] When acute GVHD occurred in allo-HSCT recipients it was associated with subsequent invasive fungal infections and a risk of increased mortality.[39] To prevent acute GVHD and infectious complications in allo-HSCT recipients, pre-engraftment reduction in bacteremia is an important step. However, there were no other risk factors identified in allo-HSCT recipients in our study, possibly because of the limited number of cases included. Our study showed that bacteremia was associated with increased morbidity in auto-HSCT recipients and increased mortality in allo-HSCT recipients. This observation was in agreement with those of prior studies showing that bacteremia had a more deleterious effect on allo-HSCT recipients relative to auto-HSCT recipients.[7,16,40]

Past studies on risk factors and outcomes of bacteremia in HSCT recipients were carried out in either auto- or allo-HSCT recipients. Our study compared the differences in characteristics and outcomes of bacteremia between allo- and auto-HSCT recipients and revealed several differences, despite identical supportive cases and prophylactic antibiotics used in agreement with previous studies.[35] Using different strategies to reduce bacteremia in allo- and auto-HSCT recipients tailored to their respective characteristics may be more cost effective than current universal prophylactic measures.

There are no previous studies that compared the clinical benefits of different doses of levofloxacin for prophylaxis in HSCT recipients. The results of our study suggested that a higher dose of levofloxacin for prophylaxis had no additional effect on the prevention of bacteremia. Since this study was retrospective in nature, rather than randomized and prospective, the results should be interpreted with caution. Additionally, suggested use of empirical antibiotics, including antipseudo penicillium, ceftazidime, and cefepime, in patients with neutropenic fever did not show promising antibacterial activity, except for carbapenem, in our study.[20] Breakthrough bacteremia involving Gram-negative bacteria was fluoroquinolone-resistant and, in most cases, also multiple-drug resistant. Our study results were in agreement with those of other studies from Taiwan that reported that fluoroquinolone prophylaxis in HSCT recipients may result in the development of fluoroquinolone-resistant and multiple-drug resistant bacteremia.[16,18] Due to the small sample size of this study, more epidemiologic data from Taiwan on bacteria isolated from HSCT recipients and continuous surveillance are required in order to guide clinicians regarding optimal empirical antibiotic use.

There were a few limitations in our study. This study was retrospective in nature, and changes in daily care that were not recorded in the medical charts may have led to confounding of the data. Definitions of bacterial infections other than bacteremia according to the Centers for Disease Control may not apply to our patients, because most were neutropenic when sepsis occurred and had few clinical symptoms. In this circumstance, therefore, the number of patients with bacterial infections may have been underestimated. Only a limited number of blood isolates were collected for analysis in this study; therefore, it is difficult to make a definitive conclusion on changes in the pattern of antibiotic resistance in HSCT recipients. Finally, the sample sizes of our two groups were relatively small, which may explain why some findings may not have reached statistical significance.

Conclusion

In conclusion, our study revealed that allo- and auto-HSCT recipients had different clinical features and outcomes. These differences should be taken into account when designing strategies to reduce the incidence of bacteremia in allo- and auto-HSCT recipients. There was also evidence of fluoroquinolone resistance and multiple-drug resistance in Gram-negative bacteria after the use of levofloxacin. It is therefore crucial to monitor changes in the patterns of antibiotic resistance in blood isolates from HSCT recipients.

Conflicts of interest

None.

Acknowledgments

This study was supported by grants from the Tri-Service General Hospital and the National Defense Medical Center (TSGH-C104-116, MAB103-M068, MAB103-M069, MAB103-M070).

References

1. Mendes ET, Dulley F, Basso M, Batista MV, Coracin F, Guimaraes T, et al. Healthcare-associated infection in hematopoietic stem cell transplantation patients: risk factors and impact on outcome. *Int J Infect Dis* 2012;**16**:e424—8.
2. Collin BA, Leather HL, Wingard JR, Ramphal R. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. *Clin Infect Dis* 2001;**33**:947—53.
3. Ninin E, Milpied N, Moreau P, Andre-Richet B, Morineau N, Mahe B, et al. Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. *Clin Infect Dis* 2001;**33**:41—7.
4. Poutsiaka DD, Price LL, Ucuzian A, Chan GW, Miller KB, Snydman DR. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. *Bone Marrow Transplant* 2007;**40**:63—70.
5. Meyer E, Beyersmann J, Bertz H, Wenzler-Rottele S, Babikir R, Schumacher M, et al. Risk factor analysis of blood stream infection and pneumonia in neutropenic patients after peripheral blood stem-cell transplantation. *Bone Marrow Transplant* 2007;**39**:173—8.
6. Mikulska M, Del Bono V, Bruzzi P, Raiola AM, Gualandi F, Van Lint MT, et al. Mortality after bloodstream infections in allogeneic haematopoietic stem cell transplant (HSCT) recipients. *Infection* 2012;**40**:271—8.

7. Pinana JL, Montesinos P, Martino R, Vazquez L, Rovira M, Lopez J, et al. Incidence, risk factors, and outcome of bacteremia following autologous hematopoietic stem cell transplantation in 720 adult patients. *Ann Hematol* 2014;**93**:299—307.
8. Gudiol C, Garcia-Vidal C, Arnan M, Sanchez-Ortega I, Patino B, Duarte R, et al. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. *Bone Marrow Transplant* 2014;**49**:824—30.
9. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev* 2012;**1**:CD004386.
10. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Bone Marrow Transplant* 2009;**44**:453—558.
11. Kimura S, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, et al. Antibiotic prophylaxis in hematopoietic stem cell transplantation. A meta-analysis of randomized controlled trials. *J Infect* 2014;**69**:13—25.
12. Kern WV, Klose K, Jellen-Ritter AS, Oethinger M, Bohnert J, Kern P, et al. Fluoroquinolone resistance of Escherichia coli at a cancer center: epidemiologic evolution and effects of discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. *Eur J Clin Microbiol Infect Dis* 2005;**24**:111—8.
13. Razonable RR, Litzow MR, Khaliq Y, Piper KE, Rouse MS, Patel R. Bacteremia due to viridans group Streptococci with diminished susceptibility to Levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. *Clin Infect Dis* 2002;**34**:1469—74.
14. Timmers GJ, Dijstelbloem Y, Simoons-Smit AM, van Winkelhoff AJ, Touw DJ, Vandenbroucke-Grauls CM, et al. Pharmacokinetics and effects on bowel and throat microflora of oral levofloxacin as antibacterial prophylaxis in neutropenic patients with haematological malignancies. *Bone Marrow Transplant* 2004;**33**:847—53.
15. Carratala J, Fernandez-Sevilla A, Tubau F, Callis M, Gudiol F. Emergence of quinolone-resistant Escherichia coli bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis* 1995;**20**:557—60. discussion 61—3.
16. Liu CY, Lai YC, Huang LJ, Yang YW, Chen TL, Hsiao LT, et al. Impact of bloodstream infections on outcome and the influence of prophylactic oral antibiotic regimens in allogeneic hematopoietic SCT recipients. *Bone Marrow Transplant* 2011;**46**:1231—9.
17. Hsueh PR, Cheng HJ, Tang JL, Yao M, Tien HF. Prophylactic use of moxifloxacin in patients receiving bone marrow transplants was not associated with increased ciprofloxacin resistance in Escherichia coli and enterococci. *Clin Infect Dis* 2005;**40**:1862—4.
18. Yeh SP, Hsueh EJ, Yu MS, Wu H, Wang YC. Oral ciprofloxacin as antibacterial prophylaxis after allogeneic bone marrow transplantation: a reappraisal. *Bone marrow transplantation* 1999;**24**:1207—11.
19. Anderson VR, Perry CM. Levofloxacin : a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* 2008;**68**:535—65.
20. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011;**52**:427—31.
21. Guidelines for the use of antimicrobial agents in patients with febrile neutropenia in Taiwan. *J Microbiol Immunol Infect* 2005;**38**:455—7.
22. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Preface. *Bone marrow transplantation* 2009;**44**:453—5.
23. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309—32.
24. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**:1813—21.
25. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2002;**34**:1094—7.
26. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing: 23th informational supplement, M100—S23*. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
27. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;**18**:268—81.
28. Hamalainen S, Kuittinen T, Matinlauri I, Nousiainen T, Koivula I, Jantunen E. Severe sepsis in autologous stem cell transplant recipients: microbiological aetiology, risk factors and outcome. *Scand J Infect Dis* 2009;**41**:14—20.
29. Mossad SB, Longworth DL, Goormastic M, Serkey JM, Keys TF, Bolwell BJ. Early infectious complications in autologous bone marrow transplantation: a review of 219 patients. *Bone Marrow Transplant* 1996;**18**:265—71.
30. To LB, Roberts MM, Haylock DN, Dyson PG, Branford AL, Thorp D, et al. Comparison of haematological recovery times and supportive care requirements of autologous recovery phase peripheral blood stem cell transplants, autologous bone marrow transplants and allogeneic bone marrow transplants. *Bone Marrow Transplant* 1992;**9**:277—84.
31. Fanning SR, Rybicki L, Kalaycio M, Andresen S, Kuczkowski E, Pohlman B, et al. Severe mucositis is associated with reduced survival after autologous stem cell transplantation for lymphoid malignancies. *Br J Haematol* 2006;**135**:374—81.
32. Offidani M, Corvatta L, Olivieri A, Rupoli S, Frayfer J, Mele A, et al. Infectious complications after autologous peripheral blood progenitor cell transplantation followed by G-CSF. *Bone Marrow Transplant* 1999;**24**:1079—87.
33. Radtke ML, Kolesar JM. Palifermin (Kepivance) for the treatment of oral mucositis in patients with hematologic malignancies requiring hematopoietic stem cell support. *J Oncol Pharm Pract* 2005;**11**:121—5.
34. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004;**351**:2590—8.
35. Hong J, Moon SM, Ahn HK, Sym SJ, Park YS, Park J, et al. Comparison of characteristics of bacterial bloodstream infection between adult patients with allogeneic and autologous hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2013;**19**:994—9.
36. Almyroudis NG, Fuller A, Jakubowski A, Sepkowitz K, Jaffe D, Small TN, et al. Pre- and post-engraftment bloodstream infection rates and associated mortality in allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis* 2005;**7**:11—7.

37. Blennow O, Mattsson J, Remberger M. Pre-engraftment blood stream infection is a risk factor for acute GVHD grades II-IV. *Bone Marrow Transplant* 2013;**48**:1583—4.
38. Poutsiaka DD, Munson D, Price LL, Chan GW, Snydman DR. Blood stream infection (BSI) and acute GVHD after hematopoietic SCT (HSCT) are associated. *Bone Marrow Transplant* 2011;**46**:300—7.
39. Fukuda T, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood* 2003; **102**:827—33.
40. Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations. *Transpl Infect Dis* 2014;**16**: 106—14.