Which Multidrug-Resistant Bacteria are Emerging in Patients with Hematological Malignancies?: One-Year Report

Habip Gedik · Funda Şimşek · Taner Yıldırım ·
Arzu Kantürk · Demet Aydın · Naciye Demirel ·
Osman Yokuş · Deniz Arıcı

Received: 17 September 2013 / Accepted: 5 May 2014 / Published online: 14 May 2014
© Indian Society of Haematology & Transfusion Medicine 2014

Abstract The aim of this retrospective, observational study was to evaluate the outcomes of bacteremia attacks during neutropenic episodes caused by chemotherapy in patients with hematological cancers by assessing mortality, involved pathogens, antimicrobial therapy and treatment responses. Patients who were older than 14 years of age and developed at least one neutropenic episode after chemotherapy to treat hematological cancer between November 2011 and November 2012 were included in the study. We retrospectively collected demographic, treatment, and survival data for 68 patients with 129 neutropenic episodes. The mean age was 59.36 ± 15.22 years (range 17–80 years), and 41 cases were male. The mean Multinational Association of Supportive Care in Cancer score was 19.56 ± 9.04 . A total of 37 (28 %) bacteremia attacks were recorded in 20 cases (29 %). Fatality rates were 50 % in the six cases with bacteremia caused by carbapenem-resistant Gram-negative bacteria; death occurred in two patients with carbapenem-resistant *Acinetobacter baumannii* and in one patient with carbapenem-resistant *Pseudomonas aeruginosa*. Clinical and microbiological responses were achieved using PIP-TAZ or CEP-SUL treatment in 80 % (16/20) of the cases with bacteremia caused by carbapenem-sensitive Gram-negative bacteria (CS-GNB). During 547 colonization-days in 21 (30 %) vancomycin-

resistant enterococci (VRE)-colonized cases among 68 patients, vancomycin-resistant *Enterococcus faecium* bacteremia developed in two patients. Non-carbapenem-based therapy can cure most bacteremia attacks caused by CS-GNB in patients with hematological cancer. However, bacteremia and other infections caused by drug-resistant pathogens, such as *A. baumannii*, *P. aeruginosa*, and VRE, are a growing concern in hematological patients.

Keywords Hematological patients · Neutropenia · Bacteremia · Antimicrobial resistance · Multi-drug-resistant bacteria

Introduction

Infection is a serious complication in patients with hematological malignancies due to immunosuppression and intensive chemotherapy. Patients who develop febrile neutropenic episodes (FNEs) due to chemotherapy for hematological malignancies should be treated as soon as possible [1]. The infectious etiology is identified in only 20–30 % of all patients with FNEs. Fever may occur and persist in 40 % of these patients despite broad spectrum antimicrobial therapy [1, 2]. The Multinational Association of Supportive Care in Cancer (MASCC) prognostic index suggests that the mortality rate is approximately 3 % if the MASCC score is >21 ; however, the mortality rate escalates to 36 % if the MASCC score is <15 [3]. Patients with bacteremia caused by Gram-negative bacteria were reported to have poor prognoses. Mortality rates were reported to be 18 % for patients with Gram-negative bacteremia and 5 % for patients with Gram-positive bacteremia [4]. Mortality rates are higher in cases with bacteremia caused by *Staphylococcus aureus* than in cases with bacteremia

H. Gedik (✉) · F. Şimşek · T. Yıldırım · A. Kantürk
Department of Infectious Diseases and Clinical Microbiology,
Ministry of Health Okmeydanı Training and Research Hospital,
S.B. Okmeydanı Eğitim ve Araştırma Hastanesi Şişli, Istanbul,
Turkey
e-mail: habipgedik@yahoo.com

D. Aydın · N. Demirel · O. Yokuş · D. Arıcı
Department of Hematology, Ministry of Health Okmeydanı
Training and Research Hospital, S.B. Okmeydanı Eğitim ve
Araştırma Hastanesi Şişli, Istanbul, Turkey

caused by enterococci and coagulase-negative staphylococci (CNS) [4]. Although CNS are isolated from blood cultures more frequently than other antimicrobial-resistant Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, the isolation of extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria has steadily increased in recent years [5, 6].

The aim of this retrospective, observational study was to evaluate the outcomes of bacteremia attacks in hematological patients during neutropenic episodes by assessing mortality, involved pathogens, antimicrobial therapy and treatment responses.

Materials and Methods

Patients in the hematology ward who were older than 14 years of age and developed at least one neutropenic episode after chemotherapy to treat hematological cancer between November 2011 and November 2012 were included in the study. This study was approved by the local ethics committee. Patients who were treated for other hematological diseases (e.g., anemia, idiopathic or immune thrombocytopenic purpura, etc.) and had not been screened with rectal swab cultures for VRE colonization while residing in the hematology ward were excluded. The hematology department was equipped with 23 beds. The patient rooms were designed as single, double and four-person rooms without high-efficiency particulate air (HEPA) filters. Patients and their attendant resided in the same room and used three shared toilets in the ward. Febrile neutropenia (FN) was defined as an oral temperature $>38.3^{\circ}\text{C}$ or two consecutive readings $>38.0^{\circ}\text{C}$ for 2 h and an absolute neutrophil count $<0.5 \times 10^9/\text{L}$ or a count expected to fall below $0.5 \times 10^9/\text{L}$ [1]. The collected data included the patients' demographics and diagnosis, neutropenic episodes, clinical presentations and laboratory findings, antimicrobial treatments, microbiological data and outcomes. In our hospital, the management of FN was based on the clinical practice guidelines of both the Infectious Diseases Society of America (IDSA) and 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) [1, 7, 8].

Blood cultures were inoculated into BactAlert 3D bottles (bioMérieux, Marcy-L'Etoile, France). Microbiological analysis of samples, including urine, sputum, wound, conjunctive, abscess, and catheter samples, was performed by inoculation onto 5 % sheep-blood agar (Salubris Inc., Istanbul, Turkey), chocolate agar (Salubris Inc.) and

MacConkey agar (Salubris Inc.). The E test method (AB BIODISK, Solna, Sweden) and the Vitek 2 automated broth microdilution method (bioMérieux) were used to perform susceptibility testing and confirmation. Clinical and Laboratory Standards Institute (CLSI 2008) breakpoints were used. Bile-esculin-azide agar plates containing 6 $\mu\text{g/mL}$ of vancomycin (Becton, Dickinson and Company, Sparks, MD, USA) were used to screen the patients for vancomycin-resistant enterococci (VRE) colonization. After inoculating rectal swabs, the plates were subsequently incubated aerobically at $35\text{--}37^{\circ}\text{C}$ with 5–10 % CO_2 for up to 48 h. Samples from the patients were cultured at two-week intervals. VRE colonization was defined as a positive culture from a rectal swab, and colonization continued until two consecutive rectal swab cultures were negative. The invasive procedures performed in VRE-colonized patients included the placement of chemotherapy port catheter lines or central line catheters and bone marrow biopsy during follow-up. Patients and their attendants were informed about resistant microorganisms and appropriate preventive measures by a nurse and doctor for 1 h each week while residing in the ward. Patients were encouraged to use alcohol-based hand disinfectant after contact with contaminated or probable contaminated materials and zones. Patients colonized with VRE resided in the same room. Health care workers were advised to use gloves and a gown when entering the room if contact with patient bodily fluids was possible. The hospital floors were cleaned daily with sodium hypochlorite (1,000 parts per million). The use of glycopeptide and anti-anaerobic antibiotics was restricted. Central line colonisation with Gram-positive bacteria was defined as presence of 15 (CFU) or more in a semiquantitative culture of distal segment of catheter tip (approximately 5 cm) using a simple pour-plate technique in patient who did not have clinical manifestations of sepsis and apparent source of blood stream infection (BSI) with blood cultures that did not grow the same microorganism.

The therapeutic regimens that were active against *P. aeruginosa* included piperacillin-tazobactam (PIP-TAZ), cefoperazone-sulbactam (CEP-SUL) and PIP-TAZ in combination with ciprofloxacin (CIP), in accordance with local antibiotic resistance status. The antibacterial treatment was changed to either imipenem or meropenem or to other antibiotics effective against bacteria grown in the sample culture if the patient exhibited a persistent fever after 2 days of empirical antibiotic therapy or had clinical, laboratory and radiological findings. Vancomycin was administered according to the previously mentioned guidelines. Patients with VRE bacteremia were treated with linezolid ($2 \times 600 \text{ mg/day}$) for at least 14 days. Patients with VSE were treated with ampicillin-sulbactam (8–12 gram/day) plus gentamycin (160–240 mg/day) for at

least 14 days. Patients who had bacteremia caused by carbapenem-resistant Gram-negative bacteria (CR-GNB) were treated with colimycin. The recommended dose of this drug is 2.5–5 mg/kg of colistin base a day, which equals 6–12 mg/kg of colistimethate sodium per day. The drug was administered as a monotherapy or in combination with another active antibiotic (e.g., rifampicin, aminoglycosides, tigecycline, etc.) for at least 14 days after receiving susceptibility results. Antibiotic doses were adjusted if the patient experienced hepatic or renal failure. Antifungal and antiviral treatments were not considered in this study, as they were not relevant to the aim and content of the study.

A response to treatment was defined as defervescence in the 48–72 h following the initiation of antimicrobial therapy and recovery of all laboratory findings or clinical symptoms associated with infection. In-hospital mortality during the neutropenic phase and the clinical outcomes of FNEs were the primary outcomes that were investigated in this study.

Statistical Analysis

Variables, including age and patient MASCC scores, were described as the mean $\pm$ SD and range. The overall 30-day crude mortality was calculated as death within 30 days of the development of neutropenia. The infection-related mortality rate was calculated as the proportion of all included patients who died in the neutropenic phase due to infection. The fatality rate was calculated as the proportion of patients with bacteremia caused by CR-GNB who died in the neutropenic phase due to bacteremia caused by CR-GNB.

Results

During the study period, 15 of 141 patients who were admitted to the hematology ward were excluded from the study based on the previously mentioned exclusion criteria. We retrospectively analyzed 68 patients, who experienced 129 neutropenic episodes (Table 1). The mean age was 60.01 ± 16.23 years (range 18–81 years), and 41 patients were male. The mean MASCC score was 19.46 ± 9.14 (Table 1). During 129 FNEs in 68 patients, 37 (28 %) episodes of bacteremia were recorded in 20 patients (29 %). Gram-negative bacteria caused 70 % (n: 26) of all bacteremia attacks. CR-GNB (n: 6) caused 23 and 16 % of Gram-negative bacteremia attacks and all bacteremia attacks, respectively. CR-GNB included *A. baumannii* (n: 4), *P. aeruginosa* (n: 1), and *Serratia marcescens* (n: 1)

Table 1 Distribution of hematologic malignancies in the patients with febrile neutropenia (n: 68)

Hematologic malignancies	n (%)
Acute myeloblastic leukemia	37 (57)
Acute lymphocytic leukemia	17 (25)
Non-Hodgkin lymphoma	4 (6)
Multiple myeloma	1 (1)
Hairy cell leukemia	2 (3)
Mantle-cell lymphoma	1 (1)
Aplastic anemia	2 (3)
Plasma cell leukemia	2 (3)
Chronic myeloid leukemia	2 (3)
Total	68 (100)

Table 2 Isolated bacteria that led to bacteremia in the patients with febrile neutropenia

Hematologic Malignancy	n (%)
ESBL (–) <i>E. coli</i>	6 (16)
Vancomycin sensitive <i>Enterococcus faecalis</i>	6 (16)
ESBL (–) <i>K. pneumoniae</i>	5 (13)
Carbapenem-resistant <i>Acinetobacter baumannii</i>	4 (11)
Carbapenem-sensitive <i>Pseudomonas aeruginosa</i>	3 (8)
ESBL (+) <i>K. pneumoniae</i>	2 (5)
ESBL (+) <i>E. coli</i>	2 (5)
Vancomycin-resistant <i>Enterococcus faecium</i>	2 (5)
Carbapenem-resistant <i>S. marcescens</i>	1 (3)
Carbapenem-resistant <i>Pseudomonas aeruginosa</i>	1 (3)
ESBL (–) <i>K. oxytoca</i>	1 (3)
Carbapenem-sensitive <i>Serratia marcescens</i>	1 (3)
MRSA	1 (3)
MSSA	1 (3)
MR-CNS	1 (3)
Total	37 (100)

ESBL extended spectrum β -lactamase, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-sensitive *Staphylococcus aureus*, MR-CNS methicillin-resistant coagulase negative staphylococci

(Table 2). The fatality rate was 50 % among six patients with bacteremia caused by CR-GNB as a result of two cases of death associated with carbapenem-resistant *A. baumannii* and one case of death associated with carbapenem-resistant *P. aeruginosa*. The hematological cancers of those patients were acute myeloid leukemia (AML) in three cases, non-Hodgkin's lymphoma (NHL) in one case, multiple myeloma (MM) in one case, and acute lymphoblastic leukemia (ALL) in one case. Those patients were undergoing antifungal treatment, but they were stable for invasive fungal infections at the time of death. All patients

with CR-GNB were followed up and isolated in the hematology ward. Screen cultures from rectal, axillary and groin sites were negative in these patients. CR-GNB developed in these patients during carbapenem therapy to treat FNEs. Central or port line catheters were removed from patients who had bacteremia caused by CR-GNB after identification. Carbapenem-resistant isolates developed during carbapenem therapy that was administered to treat FNEs (Table 2).

Clinical and microbiological responses were achieved using either PIP-TAZ or CEP-SUL therapy in 80 % (16/20) of the cases with bacteremia caused by carbapenem-sensitive Gram-negative bacteria (CS-GNB). A treatment response was achieved by switching from non-carbapenem-based beta-lactam anti-pseudomonal antibiotics to carbapenem-based therapy in four cases with bacteremia caused by ESBL-producing *K. pneumonia* (n: 2), non-ESBL-producing *Escherichia coli* (n: 1), and ESBL-producing *E. coli* (n: 1).

During 547 colonization-days in 21 (30 %) colonized cases among 68 patients, vancomycin-resistant *Enterococcus faecium*-associated bacteremia developed in two patients (Table 2). Of the two patients with VRE bacteremia, a male patient with NHL survived and a female patient with AML died of VRE bacteremia. Vancomycin-sensitive *Enterococcus faecalis* (VSE) bacteremia developed in six patients, and VSE bacteremia developed in one patient (Table 2). Of those seven patients, four were male and the median age was 44 years (range 25–73). The hematological malignancies present in those patients were AML (n: 3), ALL (n: 1), MM (n: 1), NHL (n: 1), and hairy cell leukemia (n: 1). Only two VRE-colonized patients who exhibited persistent fever accompanied with distinctive clinical findings (e.g., cough, pain in the anal region, ulcerations in oral mucosa, etc.) without confirmed VRE bacteremia were cured with linezolid therapy. The placement of chemotherapy port catheter lines and bone marrow biopsy were only invasive procedures that were performed for patients colonized with VRE during follow-up. No patient underwent intra-abdominal or urinary tract implementations.

The overall 30-day crude mortality rate was 21 % (17/68), and the distribution of hematological malignancies in patients who died included AML (n: 12), ALL (n: 4), and non-Hodgkin lymphoma (n: 1). A total of 11 patients (10 %) died of infections. Probable invasive fungal infection (n = 1) and primary bloodstream infections associated with carbapenem-resistant *A. baumannii* (n = 2), carbapenem-resistant *P. aeruginosa* (n = 1), non-ESBL producing *E. coli* (n = 2), vancomycin-sensitive *Enterococcus faecalis* (n = 2), vancomycin-resistant *Enterococcus faecium* (n = 1), *C. albicans* (n = 1) and *C. parapsilosis* (n = 1) were recorded in the patients who died.

Discussion

Bacteremia caused by Gram-negative bacteria was observed in approximately one-third of our cases during associated neutropenic episodes. Gram-negative bacteria, which colonize the gastrointestinal tract, can cause infection after passing through impaired mucosal barriers in patients undergoing chemotherapy [9]. The frequency of bacteremia attacks among neutropenic patients was reported to be between 11 and 38 % [10]. Gram-positive bacteria were reported to predominate in bloodstream infections of neutropenic patients during the 20 years after the 1960s and 1970s [5]. Gram-negative bacteria cause 24 of 30 (80 %) bacteremia attacks of our hematological patients as being consistent with reported rates [11]. Although bacteremia caused by CR-GNB was not reported in that study, carbapenem resistance rates of up to 23 % were observed among our isolates; thus, carbapenem resistance emerged more frequently than ESBL production (15 %) in our setting. The observed carbapenem resistance rates of 23 % (6/26) were notably higher than the ESBL production rates of 15 % that were observed in our hematology ward. Carbapenem therapy is likely to cause to the selection of carbapenem-resistant Gram-negative bacteria during antibacterial treatment of hematological patients [12]. The rates of carbapenem resistance observed among our bacteremia isolates were similar to the rate of 22 % that was reported in a study from Turkey [13]. Colistin monotherapy achieved clinical responses in half of patients (3/6) with CR-GNB. Colistin was used as a monotherapy due to the presence of other drugs that can cause renal impairment. In our setting, colistin and tigecycline are not used empirically to prevent selection until CR-GNB-associated infection is documented [1]. Colistin is the drug of last resort for CR-GNB-associated bacteremia and other severe infections. Hematological patients' long-term port catheters should be removed to prevent port pocket site infection, endocarditis, septic thrombosis, sepsis, tunnel infection, and persistence of bloodstream infection, even after 72 h of appropriate antibiotic treatment [1]. The observed fatality rates of 50 % demonstrate the severity of the situation. Most of the fatal cases (n: 12) and half of the cases with CR-GNB occurred in patients with AML in our study. The 30-day mortality rates associated with bloodstream infections were reported as 44.8 % for patients with carbapenem-susceptible *P. aeruginosa* bacteremia, 54.2 % for patients with carbapenem-resistant *P. aeruginosa* bacteremia, and 41 % for patients with carbapenem-resistant *A. baumannii*. [14, 15]. The severity of organ failure and leukocytosis at bacteremia onset, age, bacteremia, inadequate empiric treatment, and inadequate definitive treatment were reported to be independently associated with mortality in patients with carbapenem-

resistant *A. baumannii*-related bacteremia [16, 17]. Carbapenem resistance is increasing worldwide among Gram-negative bacteria, leading to more fatal outcomes in hematological patients and other immunosuppressed and comorbid patients. Catheters were removed in those patients because catheter removal is recommended in case of port pocket site infection, endocarditis, septic thrombosis, sepsis, tunnel infection, or persistence of BSI, even after 72 h of appropriate antimicrobial treatment [1].

The rate of ESBL production among our bacteremia isolates (20 %) was lower than those reported in other studies from Turkey, which reported infection rates of 33 and 25 % [11, 13]. While 80 % of our patients with bacteremia attacks caused by CS- GNB were treated with non-carbapenem-based beta-lactam anti-pseudomonal antibiotics, three of four (75 %) bacteremia attacks caused by ESBL-producing GNB were treated with carbapenem-based therapy. The use of beta-lactam antibiotics in combination with beta-lactamase inhibitors has been controversial in the treatment of bacteremia caused by ESBL-producing GNB yet. In a study published by Burgess et al. [18], clinical cure rates were only 55 % with piperacillin-tazobactam-based therapy. Mortality is more likely in patients with comorbidities, patients over the age of 75 years, patients residing in the ICU at bacteremia onset, patients with a non-urinary tract infection bacteremia focus and patients admitted with severe sepsis [19].

VRE colonization rates among our patients (30 %) were higher than those reported among patients with hematopoietic stem cell transplantation (HSCT) (27.5 %) and among patients with cancer (4.7 %) [20, 21]. The unfavorable conditions in our ward (e.g., shared toilets, housing of patients with their attendants, etc.) are likely to be associated with high VRE colonization rates. The observed VRE bacteremia attack rates of 9 % (2/21) among VRE-colonized patients were lower than previously reported rates, with VRE infection rates of 30 and 33 % reported in the previously mentioned studies [22]. Less invasive procedures and mild-moderate mucositis were likely to reduce the development of VRE bacteremia. Invasive devices, broad spectrum antibiotic use (i.e., vancomycin, cephalosporins, and anti-anaerobic agents) and the severity of illness were reported as independent risk factors for VRE infection [23]. Moreover, mucositis and increasing mucositis were reported to be independent risk factors for VRE-related bloodstream infection (BSI) [24]. Mortality rates were 33 % (2/6) and 50 % (1/2) in VSE and VRE bacteremia attacks, respectively. The mortality attributable to VRE bacteremia was reported to be 37 %, and the risk ratio for death was reported to be 2.3 [25]. Among our patients with VRE and VSE bacteremia, higher mortality rates were more likely to be associated with severe sepsis and septic shock compared to reported rates [25]. Antibacterial agents

that act against VRE should be initiated in hematological patients who are colonized with VRE and exhibit persistent fever and hemodynamic instability, in accordance with recommended guidelines [1, 8].

Methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *S. aureus* (MRSA) and methicillin-resistant CNS bacteremia attacks were achieved with antibacterial therapy. MRSA infections were reported to increase in patients with FN [26, 27]. Long-term catheters that are implemented to administer chemotherapy predispose patients to MRSA bacteremia and catheter infections. Patients who are admitted from health care facilities or nursing homes should be screened for MRSA colonization [28, 29].

Non-carbapenem-based therapy can cure most bacteremia attacks in hematological patients that are caused by CS-GNB. However, bacteremia and other infections caused by drug-resistant pathogens, such as *A. baumannii*, *P. aeruginosa*, and VRE, are a growing concern in hematological patients. The outcomes of this study suggest that infection control measures should be taken not only in hematology wards but also in all health care facilities with antimicrobial stewardship.

Acknowledgments We certify that there is no conflict of interest with any financial organization regarding the subject discussed in the manuscript. This study was approved by an internal ethics committee. We are greatly thankful to M. D. Onur Karatuna for his valuable recommendations about the manuscript.

References

- Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA et al (2011) Infectious Diseases Society of America. 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* 52:56–93
- Klastersky J (2004) Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis* 39(Suppl 1):32–37
- Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R et al (2000) The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 18:3038–3051
- de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F (2010) Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol* 21:252–256
- Wisplinghoff H, Seifert H, Wenzel R, Edmond M (2003) Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis* 36:1103–1110
- Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Císnal M, Sánchez-Ortega I, Duarte R, Calvo M, Carratalà J (2011) Bacteraemia due to multidrug-resistant gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. *J Antimicrob Chemother* 66:657–663
- Ascioglu S, Rex HB, De Pauw B, Bennett JE, Bille J, Croukaert F et al (2002) Defining opportunistic invasive fungal infections in

- immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 34:7–14
8. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS (2002) 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 34:730–751
  9. Blay JY, Chauvin F, Le Cesne A, Anglaret B, Bouhour D, Lasset C, Freyer G, Philip T, Biron P (1996) Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia. *J Clin Oncol* 14:636
  10. Madani TA (2000) Clinical infections and bloodstream isolates associated with fever in patients undergoing chemotherapy for acute myeloid leucemia. *Infection* 28:367–371
  11. Gedik H, Yildirmak T, Simsek F, Kanturk A, Aydin D, Arica D et al (2013) The outcome of non-carbapenem-based empirical antibacterial therapy and VRE colonisation in patients with hematological malignancies. *Afr Health Sci* 13(2):362–368
  12. Mebis J, Goossens H, Berneman Z (2010) Antibiotic management of febrile neutropenia: current developments and future directions. *J Chemother* 22:5–12
  13. Metan G, Demiraslan H, Kaynar LG, Zararsiz G, Alp E, Eser B (2013) Factors influencing the early mortality in haematological malignancy patients with nosocomial Gram negative bacilli bacteraemia: a retrospective analysis of 154 cases. *Braz J Infect Dis* 17(2):143–149
  14. Tuon FF, Gortz LW, Rocha JL (2012) Risk factors for pan-resistant *Pseudomonas aeruginosa* bacteremia and the adequacy of antibiotic therapy. *Braz J Infect Dis* 16(4):351–356
  15. Munoz-Price LS, Zembower T, Penugonda S, Schreckenberger P, Lavin MA, Welbel S et al (2010) Clinical outcomes of carbapenem-resistant *Acinetobacter baumannii* bloodstream infections: study of a 2-state monoclonal outbreak. *Infect Control Hosp Epidemiol* 31(10):1057–1062
  16. Routsis C, Pratikaki M, Platsouka E, Sotiropoulou C, Nanas S, Markaki V, Vrettou C, Paniara O, Giamarellou H, Roussos C (2010) Carbapenem-resistant versus carbapenem-susceptible *Acinetobacter baumannii* bacteremia in a Greek intensive care unit: risk factors, clinical features and outcomes. *Infection* 38(3):173–180
  17. Hernández-Torres, García-Vázquez E, Gómez J, Canteras M, Ruiz J, Yagüe G (2012) Multidrug and carbapenem-resistant *Acinetobacter baumannii* infections: factors associated with mortality. *Med Clin (Barc)* 138(15):650–655
  18. Burgess DS, Hall RG II, Lewis JS II, Jorgensen JH, Patterson JE (2003) Clinical and microbiologic analysis of a hospital's extended-spectrum beta-lactamase-producing isolates over a 2-year period. *Pharmacotherapy* 23:10
  19. Frakking FN, Rottier WC, Dorigo-Zetsma JW, van Hattem JM, van Hees BC, Kluytmans JA et al (2013) Appropriateness of empirical treatment and outcome in bacteremia caused by extended-spectrum β -lactamase producing bacteria. *Antimicrob Agents Chemother* 57(7):3092–3099
  20. Kamboj M, Chung D, Seo SK, Pamer EG, Sepkowitz KA, Jakubowski AA, Papanicolaou G (2010) The changing epidemiology of vancomycin-resistant enterococcus (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. *Biol Blood Marrow Transplant* 16(11):1576–1578
  21. Matar MJ, Tarrand J, Raad I, Rolston KV (2006) Colonization and infection with vancomycin-resistant *Enterococcus* among patients with cancer. *Am J Infect Control* 34(8):534–536
  22. Safdar N, Maki DG (2002) The commonality of risk factors for nosocomial colonization and infection with antimicrobial resistant *Staphylococcus aureus*, *Enterococcus*, gram-negative bacilli, *Clostridium difficile*, and *Candida*. *Ann Intern Med* 136:444–454
  23. Shay DK, Maloney SA, Montecalvo M, Banerjee S, Wormser GP, Arduino MJ, Bland LA, Jarvis WR (1995) Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. *J Infect Dis* 172:993–1000
  24. Kuehnert MJ, Jernigan JA, Pullen AL, Rimland D, Jarvis WR (1999) Association between mucositis severity and vancomycin-resistant enterococcal bloodstream infection in hospitalized patients. *Infect Control Hosp Epidemiol* 20:660–663
  25. Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP (1996) Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. *Clin Infect Dis* 23(6):1234–1239
  26. Kanamaru A, Tatsumi Y (2004) Microbiological data for patients with febrile neutropenia. *Clin Infect Dis* 39(Supplement 1):7–10
  27. Morris PG, Hassan T, McNamara M, Hassan A, Wiig R, Grogan L et al (2008) Emergence of MRSA in positive blood cultures from patients with febrile neutropenia—a cause for concern. *Support Care Cancer* 16:1085–1088
  28. Girou E, Pujade G, Legrand P, Cizeau F, Brun-Buisson C (1998) Selective screening of carriers for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in high-risk hospital areas with a high level of endemic MRSA. *Clin Infect Dis* 27:543–550
  29. Papia G, Louie M, Tralla A, Johnson C, Collins V, Simor AE (1999) Screening high-risk patients for methicillin-resistant *Staphylococcus aureus* on admission to the hospital: is it cost effective? *Infect Control Hosp Epidemiol* 20:473–477