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Original Article

Microbiological Profile and Predictors of Multidrug–Resistant Organisms among Cancer Patients Admitted with Bacteremia: A Retrospective Cohort Study in Jordan

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Abstract

Introduction: Bacteremia is a life–threatening complication in cancer patients. However, there are limited studies evaluating bacteremia in this patient population. The objective of this study was to evaluate the microbiological profile as well as the prevalence and predictors of multidrug–resistant organisms (MDROs) among cancer patients admitted with bacteremia.

Patients and Methods: A retrospective cohort study which included adult cancer patients admitted with bacteremia, between July 2020 and September 2022, at a comprehensive cancer center in Jordan. Patients under the palliative or bone marrow transplant services were excluded, as well as patients with blood cultures deemed as contaminants. Using the electronic medical records, patients' characteristics and the types of pathogens and susceptibilities were recorded. MDROs were defined as intrinsic or acquired non–susceptibility to at least one agent in ≥ 3 antimicrobial categories. Logistic regression was used to identify predictors of bacteremia due to MDROs.

Results: A total of 651 cases of bacteremia for 531 patients were included. The mean age of the patients was 58±16 (SD) years**,** 290 (55%) were males, and 373 (70%) had solid tumors while the remaining had hematologic malignancies. Gram–negative bacteria were reported in most cases (n = 439, 65%), the most common being *Escherichia coli* (n = 252, 57%), followed by *Klebsiella species* (n = 63, 14%). For gram–positive bacteremia, *Coagulase–negative staphylococci* were the most common (n = 64, 28%) followed by *Streptococcus species* (n = 62, 27%) and *Staphylococcus aureus* (n = 49, 21%)**.** MDROs were reported in 309 cultures (48%), with extended–spectrum–beta–lactamase–producing *Enterobacterales* and methicillin–resistant *Staphylococcus aureus* being the most common MDROs, reported in 149 (34%) and 22 (45%), of the cultures, respectively. Use of antibiotics within the previous 90 days (OR 1.5, 95% CI 1.00–2.34) and hematologic malignancy (OR 1.8 CI 1.26 – 2.67) were identified as predictors of MDRO bacteremia.

Discussion: Our study investigated the microbiological profile, prevalence, and predictors of MDRO bacteremia in a substantial cohort of adult patients with solid and hematologic malignancies admitted with bacteremia. Similar to findings from a study conducted in Lebanon, almost two–thirds of the cultures in our cohort were gram–negative. Interestingly, about half of the cases consisted of MDROs, a finding comparable to existing data as well. Additionally, we identified two predictors of MDRO bacteremia: antibiotics use within the past 90 days, which aligns with previous literature on the subject, and hematologic malignancies, which can be explained by the course of the disease, particularly the prolonged neutropenia episodes. Given the high percentage of MDROs among cancer patients with bacteremia, this study emphasizes the importance of establishing and adhering to an antimicrobial stewardship program at each healthcare institution. Furthermore, the findings of this study can serve as data sets that can be utilized to advance predictive models for MDRO bacteremia.

Conclusion: Among cancer patients admitted with bacteremia, gram–negative bacteria were the most common. About half of the bacteria were multidrug–resistant. The use of antibiotics within the past 90 days and hematologic malignancy were predictors of MDRO bacteremia. Further predictive models for MDRO bacteremia are needed to help guide the empiric antibiotic prescribing decisions.

Keywords: Bacteremia, Bacterial Multidrug Resistance, Predictors, Neoplasms, Microbiology

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Introduction

Bacteremia refers to the presence of viable bacterial microorganisms in the bloodstream, evidenced by one or more positive blood cultures, which elicit or have elicited an inflammatory response characterized by the alteration of clinical, laboratory, and hemodynamic parameters.[1] Untreated and clinically significant bacteremia progresses to systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and multi–organ dysfunction syndrome.[2]

In cancer patients with hematologic malignancies or solid organ tumors, bacteremia is recognized as a major cause of life–threatening complications.[3] In a four–year retrospective study conducted in a referral oncology hospital in Iran, Amanati et al reported bacteremia as the etiologic cause of approximately 20% to 30% of all febrile neutropenic episodes in adult patients with malignancies. Furthermore, the overall mortality rate was 21.5%.[4]

The etiology and resistance patterns of bloodstream infections are attributed to multiple factors, including patient population, the geographic region, drug resistance, and infection prevention practices at each institution.[2] In cancer patients, substantial shifts in the spectrum of pathogens isolated from blood cultures and their susceptibility patterns have been observed over the past several decades.

Between 1950s and 1960s, gram–positive bacteria were recognized as the most frequent bloodstream isolates in cancer patients. In the early 1970s, when cytotoxic antineoplastic agents were introduced, along with the introduction of beta–lactamase–resistant antistaphylococcal penicillins, gram–negative bacteria became predominating.[5,6] Moreover, a drift in the susceptibility patterns and increasing rates of antibiotic resistance have been recognized in cancer patients with bacteremia.[7–9]

Although several studies evaluated bacteremia and related risk factors within cancer patients, the majority had a relatively small sample size, included only hematologic patients or only patients with febrile neutropenia, and were conducted mostly in developing countries.[4,10–12] There is limited data describing the type of pathogens in cancer patients with bacteremia. In this study, we aimed to evaluate the microbiological profile as well as the prevalence and predictors of MDROs in adult cancer patients admitted with bacteremia at a comprehensive cancer center in Jordan.

Patients and Methods

Study Setting and Design

This was a retrospective cohort study conducted at King Hussein Cancer Center (KHCC), a 350–bed comprehensive oncology teaching center with inpatient and outpatient services, located in Amman, Jordan. The study was approved by the institutional review board, with a waiver of informed consent, due to the retrospective nature of the study.

Patients, Materials, and Definition

We included adult patients (≥ 18 years) who had positive blood cultures within 24 hours of their hospital admission, between July 2020 and September 2022. Patients with positive blood cultures were identified using our hospital's laboratory electronic system. Bacteremia was defined as having at least one positive blood culture of a gram–negative pathogen or at least two positive blood cultures of a gram–positive pathogen (except for *Staphylococcus aureus,* where one positive culture was sufficient for eligibility). Patients were excluded if they were under the palliative or bone marrow transplant services or if the blood culture was considered a contaminant. We used the College of American Pathologists (CAP) criteria to define contaminants, which included the presence of one or more of the following organisms found in only one blood culture set and only one of a series of two or three blood culture sets: Coagulase–negative staphylococci (CoNS), Micrococcus spp., viridans group streptococci, Propionibacterium acnes, Corynebacterium spp. and Bacillus spp.[13,14] In addition, if a decision of no treatment was made based on the clinical judgment documented by the physician, the blood culture was deemed as contaminant.

At our institution, two systems are used for blood cultures, the BD Bactec™ FX system, and the VersaTREK™ system, each of which has a special culture bottle. All blood cultures are collected prior to the initiation of antimicrobial therapy. A blood volume of 10 mL is drawn from adult patients into heparin–containing bottles. After collection, each bottle is placed in a separate transfer biohazard bag before leaving the patient's room and is placed into another bag with the requisition form. Specimens are kept at room temperature, not to exceed 35 degrees, then are immediately transported to the laboratory. The usual turnaround time for routine aerobic and anaerobic blood cultures is five days after incubation. When the blood culture system flags positive, gram stain would be performed and preliminary results would be notified accordingly and immediately when confirmed within one hour of detection. The number of blood culture sets to be collected depends on the clinical presentation. In the initial evaluation of febrile patients, two sets of blood cultures are usually drawn using two different venipuncture sites. In the setting of a central venous access device (CVAD), a set of blood cultures might be obtained from the line, paired with a set of blood cultures obtained through a peripheral venipuncture site. In the

setting of fever, two sets from different sites are collected prior to administration of antibiotics.

For susceptibility testing, the disc diffusion test (Kirby Bauer) as well as the E–test are two manual tests used. Two automated tests are used which include the determination of the minimum inhibitory concentration (MIC) by VITEK®–bioMérieux System and the microdilution method by Sensititre™ARIS HiQ™ System. These methods are all applied in accordance with the Clinical and Laboratory Standards Institute (CLSI) – M100 Performance Standards for Antimicrobial Susceptibility Testing last version guidelines.

The hospital–based computerized patient records system was used to collect patients' data then directly extract them into excel spreadsheets which were handled using password–protected computers. All data were double–checked by another co–investigator from the research team and if discrepancies were found, data were re–assessed by two of the co–investigators, until resolution was reached. Data collected included patients' demographics and characteristics, which consisted of age, sex, comorbidities, type of malignancy, history of previous hospitalization as well as prior use of antibiotics and high–dose corticosteroids (defined according to the Centers for Disease Control and Prevention (CDC) as a dose $\geq$ 20 mg prednisone or equivalent per day for $\geq$ 2 weeks,[15] or equipotent long–term steroids) within 90 days, surgery within the past 30 days, presence of central venous catheters (CVCs), leucocyte count, neutrophil count, presence of neutropenia, presence of febrile neutropenia (defined based on the Infectious Diseases Society of America Guidelines as the presence of a single oral temperature measurement of > 38.3 °C (101 °F) or a temperature of > 38.0 °C (100.4 °F) sustained over a 1–hour period, with an absolute neutrophil count (ANC) of < 500 cells/mm3 or an ANC that is expected to decrease to <500 cells/mm3 during the next 48 hours).[16] For each case, we also determined the etiologic microorganisms, antimicrobial susceptibility profile, symptoms at admission, empiric antibiotics, recurrence, and 30–day all–cause mortality.

Recurrence was defined as the occurrence of a new bacteremia episode after the documentation of negative blood cultures and/or completing the proper antimicrobial treatment regimen and/or having a minimum duration of 14 days between the new culture and the previous one for the same microorganism, in accordance with the literature definition and the internal KHCC antimicrobial guidelines.[17] Moreover, recurrence was further sub–classified into two main distinct groups: relapse and re–infection. Relapse referred to the recurrence of bacteremia with the same etiologic microorganism species that was present prior to treatment, whereas re–infection was defined as a recurrence of bacteremia with a different causative microorganism.[18–21]

We further classified our cohort of patients as having MDRO bacteremia or not. MDROs were defined as the intrinsic or acquired non–susceptibility to at least one agent in three or more antimicrobial categories, including beta–lactams, combinations of beta–lactams plus beta–lactamase inhibitors, cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides.[22]

Statistical Analysis

We performed descriptive analysis of the patients' characteristics. Categorical data, such as type of malignancy and sex were presented as counts and percentages. The mean, standard deviation, and/or median and range were calculated for the continuous data such as age. Differences in proportions were tested with $\chi 2$ test or Fisher exact test, and differences in continuous variables were tested with Student t test or a non–parametric test, depending on the assumptions required for each test.

A univariate analysis was used to examine the possible predictors of MDRO bacteremia. Multivariate analysis was performed for all variables that were significant on the univariate analysis, using the logistic regression model, to identify predictors significantly and independently associated with the development of MDRO bacteremia. Odds ratio values and their corresponding confidence intervals were reported for all variables included in the multivariate logistic regression. Demographic data, including age, sex, presence of comorbidities, and type of malignancy, were analyzed according to the total number of included patients, while all other variables were analyzed according to the total number of included cases. A significance criterion of $p \leq 0.05$ was used in the analysis. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). Subgroup analysis was carried out in a similar way to both cohorts, patients with hematologic malignancies and patients with solid tumors.

Results

Demographics and Baseline Characteristics

During the study period, 4598 positive blood cultures were identified, among which 651 cultures for 531 patients met the inclusion criteria. The remaining blood cultures were for patients under the palliative or bone marrow transplant services, or were considered contaminants, and were thus excluded. As 20 included cultures had more than one pathogen, the total isolated pathogens were 672.

The mean age for the included patients was 58±16 (SD) years and 290 (55%) were males. Solid tumors (n = 373, 70%) were more prevalent than hematologic malignancies (n = 158, 30%), and cardiovascular diseases were recognized as the most common underlying comorbidity amongst patients with comorbidities (n = 329, 89%), followed by endocrine and metabolic diseases (n = 240, 65%). Amongst patients who were symptomatic upon their hospital admission, respiratory symptoms were the most prevalent (n = 151, 44%), followed by urinary (n = 102, 30%) and gastrointestinal (n= 67, 20%). Piperacillin/Tazobactam was the most common empirical antibiotic (%65) with a susceptibility of %85 among the tested isolates. Other antibiotics initiated empirically were amikacin (37%), meropenem (28%), and vancomycin (28%). The baseline characteristics of patients included in the study can be found in (Table 1).

Microbiological Profile

Gram–negative bacteria were reported in the majority of cases (n = 439, 65%), with the most common being *Escherichia coli* (n = 252, 57%), followed by *Klebsiella species* (n = 63, 14%), while *Coagulase–negative staphylococci* were the most common gram–positive pathogen (n = 64, 28%) followed by *Streptococcus species* (n = 62, 27%) and *Staphylococcus aureus* (n= 49, 21%). Among our cohort of bacteremia cases (n = 651), a total of 309 cultures (48%) had MDROs. Extended–spectrum–beta–lactamase–producing *Enterobacterales*, methicillin–resistant *Staphylococcus aureus*, carbapenem–resistant *Enterobacterales*, and carbapenem–resistant *Pseudomonas aeruginosa* were found in 149 (34%), 22 (45%), 16 (4%), and 2 (7%) cultures, respectively. (Table 2) illustrates the type of bacterial pathogens isolated from blood cultures in our cohort of patients.

Predictors of Multidrug–Resistant Bacteremia

Variables that were identified by the univariate analysis to be significantly associated with the risk of developing MDRO bacteremia among all cases included: type of malignancy (solid tumors vs. hematologic malignancies), presence of CVC, antibiotic use within the past 90 days, hospitalization within the past 90 days, neutropenia, and febrile neutropenia. However, analysis using logistic

	Total (N = 651 cases)	Solid (N = 444 cases)		Hematologic (N = 207 cases)	
		MDR (N = 187)	Non–MDR (N = 257)	MDR (N = 122)	Non–MDR (N = 85)
Neutropenia (<500) upon culture collection, n (%)	151 (23)	14 (8)	22 (8.6)	72 (59)	43 (51)
Presence of febrile neutropenia upon culture collection, n (%)	126 (19)	11 (6)	18 (7.0)	65 (53)	32 (38)
Presence of Central Venous Catheter, n (%)	192 (30)	42 (23)	44 (17)	66 (54)	40 (47)
History of antibiotic use within the past 90 days, n (%)	485 (75)	142 (76)	163 (63)	108 (89)	72 (85)
History of High dose steroids within the past 90 days, n (%)	92 (14)	14 (8)	26 (10)	31 (25)	21 (25)
History of hospitalization within the past 90 days, n (%)	434 (67)	122 (65)	145 (56)	103 (84)	64 (75)
History of surgery within the past 30 days, n (%)	78 (12)	24 (13)	30 (12)	13 (11)	11 (13)
Reinfection, n (%)	72 (11)	20 (11)	21 (8)	15 (12)	16 (19)
Relapse, n (%)	43 (7)	19 (10)	7 (3)	16 (13)	1 (1)
All–Cause 30–Day Mortality, n (%)	189 (29)	63 (34)	73 (28)	32 (26)	21 (25)

Table 1. Baseline characteristics of bacteremia cases

	Type of Bacteria	Total (N = 672) n (%)	Solid (N = 461)		Hematologic (N = 211)	
			MDR (N = 193) n (%)	Non–MDR (N = 268) n (%)	MDR (N = 123) n (%)	Non–MDR (N = 88) n (%)
Gram–negative (N = 439, 65.3%)	Escherichia coli	252 (57.4)	106 (71.6)	56 (36.4)	80 (86.0)	10 (22.8)
	Klebsiella species	63 (14.4)	29 (19.6)	20 (13.0)	11 (11.8)	3 (6.8)
	Pseudomonas species	28 (6.4)	2 (1.4)	17 (11.0)	0 (0)	9 (20.5)
	Enterobacter species	17 (3.9)	3 (2.0)	12 (7.8)	0 (0)	2 (4.5)
	Acintobacter species	16 (3.6)	1 (0.7)	11 (7.2)	0 (0)	4 (9.1)
	Salmonella species	9 (2.1)	0 (0)	7 (4.5)	0 (0)	2 (4.5)
	Bacteroides species	8 (1.8)	0 (0)	7 (4.5)	0 (0)	1 (2.3)
	Campylobacter species	8 (1.8)	0 (0)	4 (2.6)	0 (0)	4 (9.1)
	Aeromonas species	7 (1.6)	1 (0.7)	4 (2.6)	0 (0)	2 (4.5)
	Others	31 (7.1)	6 (4.0)	16 (10.4)	2 (2.2)	7 (15.9)
Gram–positive (N = 233, 34.7%)	Coagulase Negative Staphylococcus species	64 (27.5)	21 (46.7)	18 (15.8)	21 (70)	4 (9.1)
	Streptococcus species	62 (26.6)	8 (17.8)	31 (27.2)	5 (16.7)	18 (40.9)
	Staphylococcus aureus	49 (21.0)	14 (31.1)	25 (21.9)	4 (13.3)	6 (13.6)
	Enterococcus species	15 (6.4)	2 (4.4)	10 (8.8)	0 (0)	3 (6.8)
	Kocuria species	9 (3.9)	0 (0)	7 (6.1)	0 (0)	2 (4.6)
	Clostridium species	8 (3.4)	0 (0)	8 (7.0)	0 (0)	0 (0)
	Others	26 (11.2)	0 (0)	15 (13.2)	0 (0)	11 (25)

Table 2. Bacterial Profile of Blood Cultures

regression found only two variables as significant independent predictors for developing MDRO bacteremia which included having a hematologic malignancy (OR 1.83, 95% CI 1.26–2.67) and the use of antibiotics within the past 90 days (OR 1.53, 95% CI 1.00–2.34).

A subgroup analysis was done for patients with solid organ tumors as well as patients with hematologic malignancies. Variables that were found significantly associated with MDRO bacteremia in patients with solid organ tumors included the following: patient's sex, and antibiotic use within the past 90 days, while in the hematologic malignancies, patient's sex and febrile neutropenia were significant. Moreover, the logistic regression model was further carried out to identify predictors of MDRO bacteremia in both cohorts, through which male sex and the use of antibiotics within the past 90 days were recognized as predictors in patients with solid organ tumors (OR 1.88, 95% CI 1.24–2.86) and (OR 1.82, 95% CI 1.20–2.77) respectively. On the other hand, female sex and febrile neutropenia were the two predictors of MDRO bacteremia in those with hematologic malignancies (OR 2.00, 95% CI 1.04–3.83) and (OR 1.89, 95% CI 1.07–3.32) respectively.

Discussion

In this study, we investigated the microbiological profile and the prevalence and predictors of MDRO bacteremia in a relatively large cohort of adult patients with solid and hematologic malignancies who had positive blood cultures identified upon their hospital admission. About two–thirds of the cultures were gram–negative and about half of the cases consisted of MDROs.

Kanafani et al. evaluated the blood stream infections in cancer patients with febrile neutropenia treated at a tertiary care center in Lebanon between 2001 and 2003.[23] The study was conducted more than a decade ago (2001–2003) and included a relatively small number of patients who had positive blood cultures (n = 33). Nevertheless, they reported findings similar to our study in that gram–negative organisms were the most common pathogens, accounting for 78.8% (26/33) of bloodstream infections in cancer patients.[23] In a 10–year longitudinal study conducted in a hospital in Saudi Arabia, positive blood cultures were reported in 13.5% of the 372 episodes of febrile neutropenia included in the study, with equal frequency of Gram–negative and

Gram–positive pathogens. In addition, it reported that, compared to patients with hematologic malignancies, patients with solid organ malignancies were less likely to have bacteremia (8.7% versus 17.1%, P = 0.042, respectively).[10] The differences in the type of pathogens among the studies could be explained in part by the type of patients included, as well as the widely known factors of geographical region and institutional–based infection prevention practices.

An interesting finding in our study was the proportion of cultures that included MDROs, which consisted of almost half of the positive cultures. This is a close proportion to that reported in the study conducted at Amir Oncology Hospital in Iran during 2018, where almost 54% of the gram–negative bacteria causing bacteremia were MDROs. In addition, the study reported a gradual increase in the incidence of MDRO bacteremia annually during their surveillance between 2015 and 2018, and indicated that this increase could be attributed to the overuse of antibiotics.[4]

In our study we identified two main independent variables as significant predictors for increased risk of developing MDRO bacteremia. The first was the use of antibiotics within the preceding 90 days of developing an MDRO bacteremia as a significant predictor, which came in alignment with previous research findings.[24] The second was hematologic malignancies, which can be related to the prolonged neutropenia episodes in patients with hematologic malignancies,[25] and the frequent use of CVCs in this patient population in order to receive chemotherapy, blood products, medications, parenteral hyperalimentation as well as for blood sampling.[26]

In addition, we performed regression analysis to identify predictors of MDRO bacteremia in both patients with solid and hematological malignancies. The two predictors of MDRO bacteremia in patients with hematologic malignancies were female sex and having febrile neutropenia. The latter can be explained by the widely known fact that the risk of bacterial infections rises significantly in cases of febrile neutropenia, particularly among patients with hematologic malignancies for which chemotherapeutic approaches are myelotoxic.[25] On the other hand, use of antibiotics in the previous 90 days and male sex were both identified as predictors of MDRO bacteremia in patients with solid organ tumors. Anatoliotaki et al. identified the previous use of antibiotics as a predictor in a retrospective study of patients with solid tumors treated at the University Hospital of Heraklion in Greece.[27] Male sex was also identified by Elenir et al. in a previous study at Texas hospitals as a relevant risk factor for presenting postoperative infections in patients with solid organ tumors.[28] Though one may expect that previous exposure to antibiotics would increase the risk of MDROs in patients with cancer, the reason behind the association of sex with MDROs is less clear. One hypothesis is that it may be related to the type of chemotherapy received for certain sex–specific malignancies that may predispose certain sex to a higher risk for MDRO bacteremia.

This study has a number of limitations. First, are the limitations related to study design being retrospective and single–centered. In addition, we elected to limit the included cases to those with positive blood cultures identified at hospital admission rather than the 48–hour time margin of hospital admission defined in literature to ensure that bacteremia was not hospital–acquired,[29,30] but this in turn might have led to misclassification bias and an underestimation of the number of true bloodstream infections and their effect size. In addition, we were unable to account for additional potential predictors for MDROs, such as the type of chemotherapy, prophylactic antibiotics, and duration of neutropenia.

Conclusion

Upon hospital admission, the majority of bacteremia cases were caused by gram–negative bacteria, with almost half of the bacteria being multidrug–resistant. The use of antibiotics within the previous 90 days and having hematologic malignancy were predictors of MDRO bacteremia. Further predictive models of MDRO bacteremia are needed to help guide the empiric antibiotic prescribing decisions.

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