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Brief report

Risk factors for multidrug-resistant bacteremia in hospitalized cancer patients with febrile neutropenia: A cohort study

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We conducted a prospective cohort study in a single tertiary hospital with the aim of assessing predictors of multidrug-resistant bacteremia in 307 cases of febrile neutropenia in adult patients with cancer. On multivariate analysis using stepwise logistic regression, age ($P = .009$), duration of neutropenia ($P = .022$), and presence of an indwelling central venous catheter ($P = .022$) were associated with bloodstream infection by multidrug-resistant bacteria.

The etiology of bloodstream infections (BSIs) in patients with cancer and febrile neutropenia (FN) has changed over the past 40 years.[1] Recently, a notable increase in antimicrobial resistance among gram-negative and gram-positive bacteria has been reported.[2] Methicillin resistance and the production of extended-spectrum beta-lactamase (ESBL) have emerged as the most frequent mechanisms of antimicrobial resistance in this setting; however, other types of multidrug resistance, including vancomycin resistance and carbapenemase production, have been described as well.[2-4] Unfortunately, few data are available concerning the risk factors for multidrug-resistant (MDR) bacteremia in the context of FN. To this end, we investigated the predictors of MDR bacteremia in adult cancer patients with FN admitted to a tertiary hospital.

METHODS

A prospective cohort study was conducted in the hematology ward of Hospital de Clínicas de Porto Alegre, which is a tertiary referral center for bone marrow transplantation in southern Brazil. We screened all consecutive subjects admitted between October 2009 and August 2011. Patients age ≥18 years with neutropenia secondary to cytotoxic chemotherapy (absolute neutrophil count [ANC] <500 cells/mm^3 or <1,000 cells/mm^3 with an expectation of decreasing to <500 cells/mm^3 over the subsequent 48 hours) and fever (a single axillary temperature measurement ≥38.5°C or temperature of ≥38.0°C sustained over a 1-hour period) were eligible for this study.

Microbiological studies were performed at the onset of fever according to standards of practice and included 2 separate blood samples from 2 different sites. In the absence of an indwelling central venous catheter, the 2 blood sets were obtained from 2 distinct peripheral veins. When an indwelling central venous catheter was present, 1 set of samples for blood culture was obtained through an indwelling central venous catheter and another set was collected from a peripheral vein. The susceptibilities of the isolated pathogens to antibiotics were evaluated according to the recommendations of the Clinical and Laboratory Standards Institute.[5] Bacteremia resulting from coagulase-negative *Staphylococcus* spp was diagnosed after 2 positive results from 2 independent cultures. Bacteraemia with one positive culture was considered diagnostic for other microorganisms. Nosocomial-acquired FN was defined as the onset of FN after 48 hours of hospitalization. Clinical comorbidity was defined by the presence of heart failure, diabetes mellitus, chronic pulmonary disease, chronic liver disease, or chronic renal failure. The grade of oral mucositis was classified according to the World Health Organization's oral toxicity scale.[6]

The primary outcome of the study was MDR bacteremia, which was defined as a BSI that was the result of methicillin-resistant staphylococci or vancomycin-resistant enterococci for gram-positive bacteria or as resistance to ≥3 classes of antimicrobial agents for gram-negative bacteria.

A stepwise backward logistic regression analysis with a limit of 0.10 was performed to determine whether the characteristics related to the host or FN episode were risk factors for BSIs caused by MDR bacteria.

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Table 1
MDR bacteria isolated in 38 cases of bacteremia in patients with FN

Microorganism	Isolates, n (%)
Gram-positive	
Methicillin-resistant coagulase-negative staphylococci	25 (65.7)
Methicillin-resistant *Staphylococcus aureus*	1 (2.6)
Vancomycin-resistant *Enterococcus faecalis*	1 (2.6)
Gram-negative	
Escherichia coli ESBL	7 (18.4)
Klebsiella pneumoniae ESBL	3 (7.8)
Enterobacter spp	1 (2.6)
Serratia spp	1 (2.6)

NOTE. There was 1 case of polymicrobial MDR bacteremia.

Table 2
Logistic regression analysis of the risk factors for MDR bacteremia in hospitalized cancer patients with FN

Variable	Cases of MDR bacteremia (n = 38)	Other cases (n = 269)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years, mean (standard deviation)	46.21 (13.0)	39.97 (14.2)	1.03 (1.006-1.05)	.013	1.03 (1.008-1.06)	.009
Female sex, n (%)	18 (47.3)	131 (48.6)	0.94 (0.48-1.87)	.878	—	
Clinical comorbidity, n (%)	15 (39.4)	61 (22.6)	2.20 (1.08-4.48)	.027	—	
Relapsing underlying disease, n (%)	18 (47.3)	137 (50.9)	0.86 (0.43-1.71)	.681	—	
ANC at diagnosis of FN, cells/mm^3, median (IQR)	170.0 (320.0)	130 (250.0)	1.0002 (0.99-1.001)	.788	—	
Duration of neutropenia, days, median (IQR)	16.5 (15.0)	8 (10)	1.02 (1.005-1.05)	.012	1.02 (1.003-1.05)	.022
Nosocomial-acquired episode, n (%)	35 (92.1)	216 (80.2)	2.86 (0.84-9.66)	.090	—	
Antimicrobial treatment in the last 30 days, n (%)	12 (31.5)	98 (36.4)	0.80 (0.38-1.66)	.560	—	
Previous hospitalization in the last 30 days, n (%)	12 (31.5)	108 (40.1)	0.68 (0.33-1.42)	.313	—	
Presence of an indwelling central venous catheter, n (%)	36 (94.7)	207 (76.9)	5.39 (1.26-23.02)	.023	5.56 (1.28-24.18)	.022
Presence of mucositis, n (%)*						
Grade I	9 (23.6)	73 (27.5)	0.65 (0.29-1.48)	.313	—	
Grade II	1 (2.6)	27 (10.0)	0.19 (0.02-1.48)	.114	—	
Grade III	1 (2.6)	15 (5.5)	0.36 (0.04-2.85)	.335	—	
Grade IV	1 (2.6)	11 (4.0)	0.49 (0.06-3.98)	.507	—	

IQR, interquartile range.
*According to the World Health Organization toxicity scale.[7]

RESULTS

A total of 307 episodes of FN were evaluated. Antibiotic prophylaxis with fluoroquinolones was not administered to any patient. During the study period, 115 BSIs were documented. The predominant pathogens were *Escherichia coli* (38.2%), coagulase-negative *Staphylococcus* spp (31.3%), *Klebsiella pneumoniae* (11.3%), *Pseudomonas aeruginosa* (9.5%), and *Streptococcus* spp (6.0%).

Among all BSIs evaluated, 38 episodes (33.0%) were caused by MDR bacteria; of these, 68.4% were caused by gram-positive bacteria, 29.0% were caused by gram-negative bacteria, and 2.6% were caused by both gram-positive and gram-negative bacteria. The MDR bacteria isolated in this study are listed in Table 1. Methicillin resistance and ESBL production were the most frequent types of antimicrobial resistance, occurring in 70.2% of staphylococci isolates and 13.5% of all gram-negative isolates, respectively.

On logistic regression analysis, age ($P = .009$), duration of neutropenia ($P = .022$), and presence of an indwelling central venous catheter ($P = .022$) were significantly associated with a BSI caused by MDR bacteria (Table 2). Each 1-year increase in age increased the risk of MDR bacteremia by 3%, and each 1-day increase in the duration of neutropenia increased the risk by 2%.

A subanalysis of the main outcome identified age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.01-1.08) and the presence of an indwelling central venous catheter (OR, 8.05; 95% CI, 1.05-61.26) as independently associated with bacteraemia caused by MDR gram-positive bacteria. In addition, the duration of neutropenia (OR, 1.04; 95% CI, 1.01-1.07) was independently associated with bacteremia caused by MDR gram-negative bacteria.

DISCUSSION

This study shows that older patients with prolonged neutropenia and patients with an indwelling central venous catheter were more likely to develop a BSI caused by MDR bacteria. In particular, age and the presence of an indwelling central venous catheter were associated with gram-positive MDR bacteremia, whereas prolonged neutropenia was associated with gram-negative MDR bacteremia.

Although our results seemingly differ from those of previous studies, the published studies of risk factors for MDR bacteremia in patients with FN are heterogeneous, with differences possibly reflecting the influence of local epidemiology. In a prospective multicenter study of 91 hematopoietic stem cell transplant recipients with BSI, Oliveira et al[7] found an association between previous exposure to third-generation cephalosporins and an increased risk of MDR gram-negative bacteremia. Our institution has a policy of restricted third-generation cephalosporin use, effective in 2003. In a study of 239 episodes of bacteremia (75% gram-positive organisms and 25% gram-negative organisms) in children with cancer and FN, El-Mahallawy et al[8] found that reduced ANC, previous exposure to antibiotics, and particularly prolonged duration of neutropenia (>7 days) were associated with BSI due to MDR gram-negative bacteria. In contrast to these previous studies, our study identified the presence of an indwelling central venous catheter as a risk factor for a BSI due to MDR gram-positive bacteria, which may be explained by the high incidence of methicillin-resistant coagulase-negative staphylococci in our institution. In addition, the finding that age and prolonged neutropenia were risk factors for a BSI due to MDR bacteria has scientific plausibility, given that both factors are associated with decreased host response to infection.

Our findings suggest that improving preventive measures to avoid catheter-related infections and the appropriate use of less-cytotoxic chemotherapy regimens with short periods of neutropenia could result in effective strategies to prevent MDR bacteremia in patients with FN.

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