Bloodstream infections and mortality-related factors in febrile neutropenic cancer patients

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background:
We performed a prospective observational cohort study to evaluate the causative bacteria and to identify risk factors for mortality in febrile neutropenic (FN) patients with blood stream infection (BSI).

Material/Methods:
We conducted a prospective data collection on all patients with bacteremia or fungemia. The patients were assigned into low-risk and high-risk groups in accordance with the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index.

Results:
Throughout the study period, the patients developed 420 FN episodes. Out of 420 episodes, only 90 (21.4%) were found to have bloodstream infection. The mean age of the patients was 45.6±18.4 years and 55.6% of the patients were male. A total of 98 isolates were recovered from the cases of BSI. Coagulase-negative Staphylococcus spp (CoNS) were the most common isolates overall (33.7%). There was a significant increase in the rate of gram-negative bacteria throughout the study period (p=0.028). Overall mortality was 33%. Multivariate analyses showed that MASCC risk scores (p=0.0001, OR=15.1, CI%95 4.5-50.7), ICU wards (p=0.0002, OR= 8.6, Cl%95 1.101-68,157) and CoNS (p=0.004, OR=12.12, CI%95 2.3-64.7) were independent risk factors associated with mortality. BSI due to CoNS was associated with lower mortality; however, MASCC high risk score and ICU stay were associated with higher mortality.

Conclusions:
The MASCC risk-index score and emergence of CoNS in positive blood cultures are valuable tools in the management of FN.

key words: bloodstream infection • febrile neutropenia • mortality

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BACKGROUND

Chemotherapy-induced neutropenia is a major adverse effect of cancer treatment. Bacteremia (BSI) was documented in blood cultures (BC) in 11–30% of the febrile neutropenia (FN) episodes [1–5]. The mortality from FN may be as high as 10%, depending on the population studied, and FN is still responsible for the majority of chemotherapy-associated deaths [6–8]. It includes a spectrum of clinical syndromes ranging from non-infectious fever to severe life-threatening infections. Patients with FN and bacteremia form a small subgroup within this spectrum, including severely infected patients. The epidemiology of bacteremic febrile neutropenia constitutes the basis for selection of empiric antibiotic therapy for febrile neutropenia [9]. There has been a shift from the predominance of gram-negative bacteria to predominance of gram-positive bacteria in many centers over the past 2 decades [10–13]; however, in recent years there has been a reverse of this trend in several centers. In fact, these centers reported the re-emergence of gram-negative bacteria in febrile neutropenic patients [14,15]. The significant variability between locations requires investigation of local trends to guide more appropriate antibiotic treatment.

Therefore, we performed a prospective cohort study to evaluate the causative bacteria and to identify risk factors for mortality in febrile neutropenic patients with BSI.

MATERIAL AND METHODS

This was a prospective observational cohort study. All patients with bacteremia or fungemia (thereafter referred to as bacteremia) and neutropenia (absolute neutrophil count of <500/mm³) consecutively hospitalized between December 2004 and December 2009 were included. Our hospital, Mersin University Faculty of Medicine, is a 402-bed tertiary-care, general medical ward of a general hospital, in Mersin, Turkey. Patients' malignancies were treated with chemotherapy except in cases of stem cell transplantation. All patients with febrile episodes were evaluated and treated according to current guidelines by an infectious disease specialist. Prophylactic antibiotics was not used, but growth factor was used when necessary [16].

The patients were assigned into low-risk and high-risk groups in accordance with the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index [17]. Those with a score of ≥21 were classified as low risk and those with a score of <21 classified as high risk [17]. All patients had a solid or hematologic malignancy. Mortality was defined as all-cause in-hospital mortality up to 30 days after BSI. BSI developing after 48 hours in hospital was considered as hospital-acquired.

Blood cultures were performed using the BACTEC 9240 (Becton Dickinson, Franklin Lakes, NJ, USA) automated system. Sensitivity to antibiotics was tested by the disk diffusion method on Mueller-Hinton agar according to Clinical and Laboratory Standards Institute (CCLS) procedures. Biological isolates were identified with the help of API (Bio Merieux SA Marcy I'Etoile, France). At least 2 positive cultures were required to define a bacteremia due to coagulase-negative staphylococci as a BSI.

Table 1. Distribution of the patients according to diagnosis.

	Patients diagnosis (n=90)
Solid malignancies (n=12)	Gastrointestinal system (5)
	Lung (3)
	Skin soft tissue(2)
	Mammary glands(1)
	Brain (1)
Hematologic malignancies (n=78)	Acute myeloid leukemia (41)
	Acute Lymphoblastic Leukemia (15)
	Hodgkin Diseases(5)
	Non-Hodgkin Lymphoma(5)
	Chronic Lymphoblastic Leukemia (7)
	Multiple myeloma(3)
	Chronic Myeloblastic Leukemia(2)

Methicillin-resistant s*taphylococcus aureus* (MRSA), vancomycin-resistant *enterococcus spp.* (VRE), *pseudomonas aeruginosa, acinetobacter baumannii* and *stenotrophomonas maltophilia* resistant to at least 3 different groups of antibiotics and extended spectrum beta-lactamase (ESBL) producing gram-negative bacilli were considered as multiple drug resistant (MDR) bacteria.

Statistical analysis

The SPSS 11.5 (Chicago, IL) package program was used for statistical analysis. Univariate statistical analysis including Student's t test was used for continuous data. Chi-square and Fisher's exact test were used for categorical data. P values of <0.05 were considered significant. Multivariate logistic regression analysis was performed to determine risk factors independently associated with mortality.

RESULTS

Throughout the study period, the patients developed 420 febrile neutropenic episodes. Out of 420 episodes, only 90 (21.4%) were found to have BSI. The mean age of the patients was 45.6±18.4 years and 55.6% of the patients were male. The median time to development of BSI was 9.4±10.7 days (range 1–63). A total of 98 isolates were recovered from the cases of BSI. Polymicrobial bacteremia was detected in 6 episodes (6.7%). Forty-nine patients (54.4%) were in the low-risk group, 78 (86.7%) had hematogenous malignity, and 12 patients (13.3%) had solid malignancies. Thirty patients died. Of total bloodstream infections, 59.1% were nosocomial, and the most frequent underlying type of malignancy was AML (n=41). Table 1 shows the distribution of the patients by their diagnoses.

Gram-positive bacteria were more frequently isolated than gram-negative bacteria throughout the study period. Table 2 shows the distribution of causative bacteria. Coagulase-negative *Staphylococcus* (CoNS) spp. was the most common bloodstream isolate overall (33.7%), followed by

Table 2. Microorganism (n=98) causing positive blood cultures in febrile neutropenic patients, 2004–2009.

Microorganisms	No. (n MDR)
Monomicrobial	
Gram negative, total	**44**
E. coli	21 (8)
P. aeruginosa	6
K. pneumoniae	4
A. baumannii	9 (9)
Enterobacter spp.	2 (2)
Serratia spp.	2
Gram positive, total	**47**
Coagulase-negative *Staphylococcus* spp.	33 (18)
S. aureus	7 (3)
Enterococcus spp.	4
α-*Hemolytic streptococci*	1
Streptococcus pneumoniae	2
***Candida* spp. total**	**7**
C. albicans	2
C. non-*albicans*	5
Polymicrobial	
Only Gram-positive organisms*	3
Both Gram positive and Gram negative organisms**	3

* Infection with the following: (1) *S. aureus* and coagulase-negative *Staphylococcus* spp.; (2). *S. aureus* and coagulase-negative *Staphylococcus* spp.; (3) *S. aureus*, Metisilin-sensitive coagulase-negative *Staphylococcus* spp. and Metisilin-resistant coagulase-negative *Staphylococcus* spp.; ** Infection with the following: (1) *E. coli* and, *S. aureus*; (2) *E. coli*, Metisilin-sensitive coagulase-negative *Staphylococcus* spp. and Metisilin-resistant coagulase-negative *Staphylococcus* spp.; (3) *Enterococcus* spp.and *P. aeruginosa*.

E. coli (21.4%). Gram-negative bacteria were found in 30.7% of the isolates in 2004 and 2005, 42.8% of the isolates in 2006 and 2007, and 62.8% of the isolates in 2008 and 2009. The distribution of BSI episodes (n=90) according to study years were 26 episodes (28.9%) in 2004–5; 21 (23.3%) episodes in 2006–7 and 43 (47.8%) episodes in 2008–9. Percent of gram-positive bacteremia (n=42) according to study years were 18 (42.9%) episodes in 2004–5; 10 (23.8%) episodes in 2006–7, and 14 (33.3%) episodes in 2008–9. Occurrence of gram-negative bacteremia (n=44) according to study years was 8 (18.2%) episodes in 2004–5, 9 (20.5%) episodes in 2006–7, and 27 (61.4%) episodes in 2008–9 (Figure1). There was a significant increase in the rate of gram-negative bacteria throughout the study period (p=0.028); in fact, there was a striking increase, especially in the rate of acinetobacteria
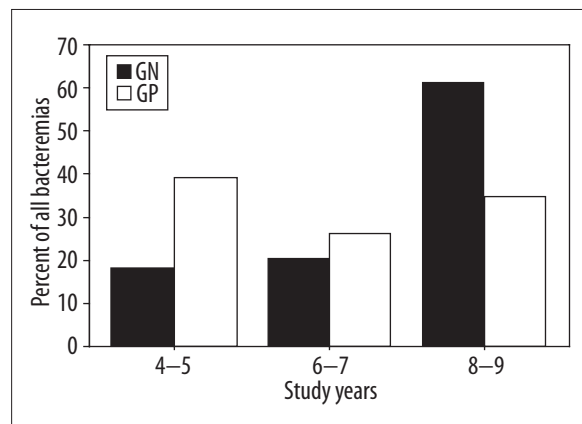
Figure 1. Percent of gram positive and gram negative bacteremia throughout the study period.
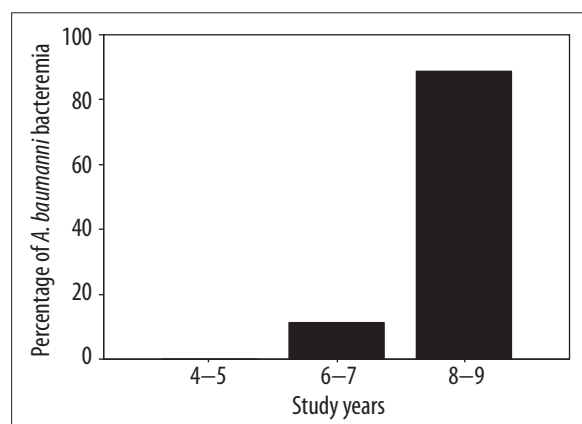
Figure 2. Increase in *A. baumanni* bacteremia throughout the study period.

(p=0.029). Acinetobacteria were not found (0%) in the first 2 years of the study, comprised 4.7% of the isolates in the second 2 years of the study, and 18.6% of the isolates in the third 2 years of the study (Figure2). Thirty-five microorganisms isolated (35.7%) were MDR.

Univariate analyses (Table 3) showed a significant relation between mortality and MASSC scores (p=0.000) and several characteristics of causative agents. The relation between mortality and gram-negative bacteria, acinetobacteria, non-fermentative bacteria, stay in intensive care unit (ICU) wards and coagulase-negative staphylococci (CoNS) was significant (p=0.002, 0.005, 0.009,0.002,0.0001, 0.0001, respectively).

Multivariate analyses showed that MASSC scores (p=0.0001, OR=15.1, CI%95 4.5–50.7), stay in ICU wards (p=0.0002, OR= 8.6, Cl%95 1.101–68,157) and CoNS were independent risk factors associated with mortality (p=0.004, OR=12.12, CI%95 2.3–64.7) (Table 3). BSI due to CoNS was associated with lower mortality; however, MASCC high risk score and ICU stay were associated with higher mortality.

DISCUSSION

Our study found that 21.4% of the febrile neutropenic patients with cancer had BSI. This is consistent with other

Table 3. Risk factors for mortality in febrile neutropenic cancer patients with BSI by univariate and multivariate analysis.

Univariate analysis	Nonsurvivors (n=30)	Survivors (n=60)	p value
Age (years)	45.2±18.1	45.8±18.6	0.897
Male/Female gender	18/12	32/28	0.549
Hospital stay(day)	27.4±17.5	34.8±27	0.308
MASSC score Low-risk group (≥21) (n=49) High-risk group (<21) (n=41) High-risk group <15 (n=13)	5 25 10	44 16 3	0.0001 0.0001 0.0001
Etiologic agents Gram positive bacteremia (n=42) Gram negative bacteremia (n=44)	7 21	34 23	0.002 0.005
Nonfermentative bacteremia (n=13)	9	4	0.002
CoNS bacteremia (n=29)	2	27	0.0001
ICU wards (n=11)	9	2	0.0001
Nosocomial BSI (n=26)	13	13	0.717
Multivariate analysis	**OR (95% CI)**		**p value**
MASCC score index	15.1 (4.5–50.7)		0.0001
CoNS bacteremia	12.12 (2.3–64.7)		0.004
ICU wards	8.6 (1.101–68,157)		0.002
Gram negative bacteremia	1.2 (0.449–68.9)		0.181
Nonfermentative bacteremia	1.1(0.064–22.43)		0.903

reports showing that up to 30% of the episodes of FN are associated with confirmed bacteremia [5,6–18]. The most commonly isolated bacteria in the present series were CoNS, which accounted for 33 of 98 (33.7%) blood culture isolates, similar to other studies [5,19].

Overall, gram-positive organisms accounted for nearly 50% (n=47, 47.9%) of all blood culture isolates. These data support the documented high rates of gram-positive infections in cancer patients with FN [6–19]. In fact, prior studies revealed that 50%-71% of the etiological agents found in microbiological analyses in FN patients with BSI were gram-positive bacteria [5,21,22,23]; however, the rate of gram-negative infections is on the rise in some centers [24,25,26]. Recently, non-fermentative gram-negative rods such as *Acinetobacter* species have appeared as pathogens in FN patients [20,21].

Although the most frequent causative agents were gram-positive bacteria throughout the study period, there was a significant increase in gram-negative bacteria, especially acinetobacteria, in the last 2 years of the study; 30.7% and 62.8% of the isolates had gram- negative bacteria in the first and the last 2 years of the study, respectively. Recently, Chen et al reported that gram-negative bacteria were the predominant pathogens (60%) and that fungi were relatively uncommon (6%) in bloodstream infections in patients with neutropenia. In addition, the number of Acinetobacter and Stenotrophomonas infections increased from 2002 to 2006,

and were the third (7%) and fourth (6%) most frequent after *E. coli* and *Klebsiella* [27].

A. baumannii and *S. maltophilia* were found in 1–3% of the bloodstream isolates from neutropenic patients in the USA and Europe [22,28]. However, in some areas the frequency of *A. baumannii* complex in neutropenic patients is reportedly higher, at 6–9% [21,24,29]. According to data from the infection control committee of our hospital, there has been an increase in acinetobacteria resistant to multiple antibiotics in the past few years. This increased rate of acinetobacteria in FN patients can be attributed to nosocomial transmission.

Our multivariate analysis revealed that isolation of a CoNs strain and MASSC index-score are independent predictors of mortality in patients with FN and BSI. Uys et al showed that the MASCC risk-index score correctly identifies low- and high-risk patients at presentation with febrile neutropenia [30]. This study showed that the MASCC risk-index score had a positive predictive value of 98.3% and a negative predictive value of 86.4%, with both a sensitivity and specificity of 95%.

We found that mortality was 10.2% in the low-risk patients with the MASSC score of 21 and above and 60.8% in the high-risk patients (p=0.000). Consistent with the results of the present study, Klastersky et al. [22] reported a relatively low rate of overall complications (18%) and death (3%)

in low-risk patients with bacteremia and MASCC scores of >21, but that when the MASCC score was <21, the corresponding figures were 49% and 19% (*P*<0.001). When the score was <15, overall complications (79%) and mortality (36%) were even higher. In fact, when the score was 15–20, the rates of complications and mortality were 40% and 14%, respectively. In our study, 13 patients had a MASCC score index <15. Mortality rate was higher (76.9%) in this group. This results was statistically significant (p=0.0001) and similar to the results of Klastersky's study. Based on MASSC scores, low-risk and high-risk patients with BSI can be identified easily, and, accordingly, an appropriate therapy can be given to the high-risk patients in order to decrease the very high overall complication and mortality rates seen in these patients [22]. We also found that CoNS bacteremia was a predictor of a very low mortality (6.9%). Klastersky et al. found a mortality of 6% in patients with CoNS and a higher mortality of 18% in patients with gram-negative bacteria (p<0.001). In the present study, the mortality was 16% in patients with gram-positive bacteremia, but 47% in patients with gram-negative bacteremia.

Prior studies have revealed that gram-negative bacteremia is usually associated with higher case fatality rates than gram-positive infections, and that the risk is further increased due to antimicrobial resistance if effective treatment is delayed [23,31–34].

In the present study, 43.2% of gram-negative bacteria were multi-drug resistant, and 20.5% of these bacteria were highly resistant bacteria such as acinetobacteria. This might have contributed to the increase in the mortality due to gram-negative bacteria. In addition, gram-positive bacteria are isolated easily and quickly; therefore, they are easily identified, which allows treatment. This may explain the low mortality from gram-positive bacteria.

CONCLUSIONS

There has been an increase in the rate of bloodstream infections due to antimicrobial- resistant gram-negative bacteria in FN patients. Bacterial epidemiology and antimicrobial resistance in these patients should be regularly monitored, which will provide guidance for local policies for the use of antimicrobial agents and the assist in the choice of agents for empirical antibiotic therapy and prophylaxis in FN patients. The MASCC risk-index score and emerging of CoNS in positive blood cultures are valuable tools in the management of patients with febrile neutropenia, and can be used to accurately predict mortality in patients with BSI.

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