

# The relationship between mortality and microbiological parameters in febrile neutropenic patients with hematological malignancies

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## ABSTRACT

**الأهداف:** لتحديد عوامل الخطر الفعالة على الوفيات في حالات العدلات الحموية مع الأورام الخبيثة الدموية. المرضى الذين يعانون من أمراض الدم أكثر عرضة للعدوى، وهذه هي أسباب متكررة للوفيات.

**الطريقة:** أجريت هذه الدراسة بأثر رجعي باستخدام بيانات من 164 حالة الحمى القلوية مع الأورام الخبيثة الدموية الذين تمت متابعتهم في عيادة أمراض الدم في مركز الرعاية الصحية العالي بين 2011-2015. تم بحث العلاقة بين المعدلات الوصفية والسريرية ومعدلات الوفيات في اليومين السابع واليوم الواحد والعشرين.

**النتائج:** المرضى الذين يعانون من العدلات المطلقة أقل من 100 /م<sup>3</sup>، ومدة قلة العدلات أطول من 7 أيام، والالتهاب الرئوي أو بؤر الجهاز الهضمي من العدوى، والقسطرة المركزية ( $p=0.025$ )، وعزل البكتيريا جرام (-) في الثقافة، ومقاومة الكاربابينيم، والصدمة الإنتانية وكان نمو البكتيريا أثناء المعالجة الوريدية للمضادات الحيوية أكثر عرضة للوفيات في كل من اليومين السابع واليوم الحادي والعشرين. أظهرت نتائج الانحدار اللوجستي متعدد المتغيرات النهائية أن الالتهاب الرئوي ( $p<0.0001$ )، والصدمة الإنتانية ( $p=0.004$ ) وعزل البكتيريا سالبة الجرام ( $p=0.032$ ) كانت عوامل خطر ذات دلالة إحصائية.

**الخاتمة:** التشخيص المبكر والعلاج المناسب للالتهابات خطيرة، والتي هي من الأسباب الهامة للمرض والوفيات، حاسمة في المرضى الذين يعانون من قلة العدلات الحموية. وبالتالي، يجب على كل مركز متابعة عن كثب أسباب العدوى ووضع بروتوكولات العلاج بالمضادات الحيوية التجريبية لتحقيق نتائج أفضل في التحكم بقلّة العدلات الحموية.

**Objectives:** To determine effective risk factors on mortality in febrile neutropenic cases with hematologic malignancy. Patients with hematologic diseases are more prone to infections and those are frequent causes of mortality.

**Methods:** This retrospective study was performed using data of 164 febrile neutropenic cases with

hematologic malignancies who were followed up in a hematology clinic of a tertiary health care center between 2011-2015. The relationship between descriptive and clinical parameters rates and rates of mortality on the 7<sup>th</sup> and the 21<sup>st</sup> days were investigated.

**Results:** Patients with absolute neutrophil count  $<100/\text{mm}^3$ , duration of neutropenia longer than 7 days, pneumonia or gastrointestinal foci of infection, central catheterization ( $p=0.025$ ), isolation of Gram (-) bacteria in culture, carbapenem resistance, septic shock, and bacterial growth during intravenous administration of antibiotic treatment were under more risk for mortality on both the 7<sup>th</sup> and the 21<sup>st</sup> days. The final multivariate logistic regression results showed that pneumonia ( $p<0.0001$ ), septic shock ( $p=0.004$ ) and isolation of Gram-negative bacteria ( $p=0.032$ ) were statistically significant risk factors.

**Conclusion:** Early diagnosis and appropriate treatment of serious infections, which are important causes of morbidity and mortality, are crucial in patients with febrile neutropenia. Thus, each center should closely follow up causes of infection and establish their empirical antibiotherapy protocols to accomplish better results in the management of febrile neutropenia.

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Infection is the most important cause of morbidity and mortality in patients with hematologic malignancies. Nowadays, the development of intensive chemotherapy protocols and interventional procedures have resulted a serious increase in cure rates of the patients, while immunosuppression caused by these treatments also enhances incidence rates of infection.<sup>1,2</sup> The relationship between fever and infection in neutropenic patients was defined during the 1960s. Initially, this rarely encountered relationship was described as a serious clinical entity after more widespread and intensive use of cytotoxic drugs and its treatment was started thanks to developed guidelines.<sup>3</sup>

Neutropenic fever is a condition which may lead to fatal complications in patients receiving chemotherapy, stem cell transplantation or immunodeficient states. In all neutropenic patients, the cause of fever may not be an infection, in this patient group fever may encounter us as the most important and sometimes the only symptom of infection. Because of the defects in host defense, lack of adequate inflammatory response to microorganisms causing infection that leads to an inability to detect signs and symptoms of infection in these patients which are expected to become manifest under normal conditions.<sup>3,4</sup>

Neutropenia has been defined as the anticipated condition where the absolute number of neutrophil counts in peripheral blood is below 500/mm<sup>3</sup> or between 500-1000/mm<sup>3</sup> which drops below 500/mm<sup>3</sup> within 48 hours. Severity and duration of neutropenia markedly affect the risk of infection.<sup>3,4</sup> Factors such as severe neutropenia (neutrophil counts, <100/mm<sup>3</sup>), a rapid drop in neutrophil counts, duration of neutropenia more than 10 days markedly increase the probable risk of development of infection.<sup>5</sup> Still, longer hospital stay and underlying primary disease of the patient also affect the development of infection.<sup>6,7</sup>

The body temperature of  $\geq 38.3^{\circ}\text{C}$  was measured once from the oral or axillary route or body temperature of  $38.0\text{-}38.2^{\circ}\text{C}$  persisting for one hour was defined as neutropenic fever.<sup>1-4</sup> Since pathogenic agents are frequently of endogenous origin and polymicrobial in neutropenic patients, foci or agents of infection cannot be identified.<sup>7,8</sup>

In patients with hematologic malignancies, intensive chemotherapy protocols increase both response rates and survival times. However, the frequency of neutropenic infection and hospital stays increase due to intensive

chemotherapy protocols. In neutropenic patients, classical findings of infections may not be seen depending on decreased inflammatory response. In these patients, fever is the first and frequently the only indicator of infection. In patients who developed chemotherapy-related febrile neutropenia (FEN), infection is the most important cause of mortality. Therefore, in neutropenic patients presence of fever is accepted as an emergency medical condition. Nowadays, as a standard approach, fever should be considered of infection origin, and prompt initiation of empirical treatment with broad-spectrum antibiotics should be initiated in neutropenic febrile patients unless proved otherwise. Mortality rates up to 75% in patients who developed FEN, decreased dramatically after the empirical use of broad-spectrum antibiotics were initiated.<sup>3</sup> In FEN patients, many factors including primary disease of the patient, immunological state, organ functions, chemotherapy protocols applied, severity and duration of neutropenia play a role in the selection of antibiotherapy in FEN patients.

Fever without any demonstrable microbiological, clinical and laboratory evidence of infection is termed as isolated fever.<sup>9</sup> Healthcare centers should closely monitor their own agents of nosocomial infections and determine their own empirical antibiotherapy protocols which may contribute favorably to the more improved management of this process. To this end, in our study, infection categories, bacterial isolates, mortality rates and antibiotherapies applied were evaluated. The correlation between mortality and parameters related to demographic, clinical, microbiological, antibiotherapy was analyzed.

**Methods. Study design.** This study was performed in the Hematology Department of our tertiary care center, Izmir, Turkey, following the approval of the local Institutional Review Board. A retrospective analysis was performed on data derived from the medical files of 164 patients diagnosed with hematologic malignancies in the hematology Department of our tertiary care center, Izmir, Turkey, between 2011-2015. There was no informed consent.

**Exclusion criteria.** Patients who were admitted to the hospital for other haematological diseases such as hemolytic anemia, idiopathic thrombocytopenia, hemophilia or coagulation disorders were excluded.

Diagnosis of hematological malignancy was made based on an evaluation of clinical findings, whole blood count, peripheral smear, bone marrow aspiration or biopsy, histochemical staining, flow cytometry and cytogenetic assessment. Without any environmental factor, one-time measurement of body temperature as

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$\geq 38.3^{\circ}\text{C}$ , or body temperature of  $38.0\text{-}38.2^{\circ}\text{C}$  persisting for one hour was accepted as fever conditions both with neutrophil counts are below  $500/\text{mm}^3$  or neutrophil counts between  $500\text{-}1000/\text{mm}^3$  but expected to drop below  $500/\text{mm}^3$  within 24-48 hours were evaluated as neutropenia.<sup>9</sup>

In Izmir Bozyaka Training and Research hospital, Izmir, Turkey, phoenix automated system is used for culture. We worked in compliance with The Clinical & Laboratory standards institute (CLSI) criteria. *Coagulase-negative Staphylococci* spp. or *Corynebacterium* spp. were accepted as a pathogenic agent if these microorganisms grew in 2 blood culture media or one blood culture media in cases where fever could not be related to another cause. Blood culture positivity was defined as growth of a known pathogenic microorganism on at least one blood culture media.

In Izmir Bozyaka Training and Research hospital, Izmir, Turkey, fluoroquinolone prophylaxis was not performed due to a potential role of selecting for, extended spectrum beta-lactamase (ESBL)-producing and fluoroquinolone-resistant *Enterobacteriaceae*. According to neutropenic fever protocol applied, if the patient has a stable clinical status without any signs of pneumonia or soft tissue infections, then monotherapy is preferred. The first alternative is piperacillin-tazobactam dose escalation may be made based on the clinical state of the patient. If the patient is not in a stable clinical condition and has hypotension or pneumonia, then meropenem or imipenem was preferred in empirical treatment. If the patient has signs of pneumonia and soft tissue infection an antibiotic effective on Gram-positive bacteria was included in the empirical treatment.

If a microorganism of normal skin flora grows, then the onset of fever at least once when antimicrobial treatment started or detection of growth in at least 2 sets of blood cultures in the presence of hypothermia, intravenous catheter, shivering or hypotension then this microorganism was accepted as a significant pathogen.<sup>9</sup>

Descriptive and clinical features such as age, gender, diagnosis, co-morbidities, duration of hospitalization, deepness of neutropenia and the presence of central venous catheters were investigated. Also, survivals of patients at the end of the 7<sup>th</sup> and the 21<sup>st</sup> day were noted.

**Outcome parameters.** In the present study, we investigated the relationship between rates of mortality on the 7<sup>th</sup> and the 21<sup>st</sup> day and descriptive and clinical parameters aforementioned above. Furthermore, the association between mortality and microorganisms isolated in cultures, resistance against ESBL, carbapenem and methicillin and presence of infectious foci such as pneumonia and catheter on mortality were evaluated.

**Statistical analysis.** Statistical Package for the Social Science version 20 (IBM, Corp., Armonk, NY, USA)

was used for the analysis of data. For quantitative data mean, standard deviation, minimum and maximum values; while frequency values were tabulated for qualitative data. For the comparison of categorical data, Pearson chi-square, and Fisher's Exact tests were used. Data were evaluated at a level of 95% confidence level, A  $p\text{-value} < 0.05$  was considered significant. Parameters found to be statistically significant in the univariate analyses that were evaluated in a multivariate logistic regression to predict the risk of mortality.

**Results.** Study participants consisted of 94 (57.3%) male and 70 (42.7%) female patients. The average age of patients in our series was  $54.2 \pm 15.7$  (range=18-84). The patients were either younger than 60 years ( $n=93$ ) (56.7%) or  $\geq 60$  years of age ( $n=73$ ) (43.3%). The total duration of neutropenia was  $7.8 \pm 8.1$  days (range=1-45), while the day on which neutropenia was diagnosed after hospitalization was  $14.6 \pm 12.6$  (range=1-55). In this series, septic shock was detected in 22 (13.4%) and *polymicrobial* bacteremia was identified in 7 (4.2%) cases. Rates of mortality on the 7<sup>th</sup> and the 21<sup>st</sup> day were 42 (21.6%) and 58 (35.4%).

Table 1 presents an overview of our baseline data. Accordingly, the most frequent hematological malignancies were acute myeloid leukemia, non-Hodgkin lymphoma, and acute lymphocytic leukemia. The most common foci of infection were primary bacteremia, pneumonia, and cutaneous infections. Microorganisms isolated in culture studies and antibiogram profiles are especially given in detail in Table 2.

In Table 3, results of the analysis of the relationship between parameters under investigation and mortality rate on the 7<sup>th</sup> day and 21<sup>st</sup> day were demonstrated. Patients with absolute neutrophil count  $< 100/\text{mm}^3$  ( $p=0.014$ ), duration of neutropenia longer than 7 days ( $p=0.003$ ), pneumonia or gastrointestinal foci of infection ( $p < 0.001$ ), central catheterization ( $p=0.025$ ), isolation of Gram (-) bacteria in culture ( $p=0.003$ ), carbapenem resistance ( $p < 0.001$ ), septic shock ( $p < 0.001$ ), and bacterial growth during intravenous administration of antibiotic treatment ( $p < 0.001$ ) were under more risk for mortality on the 7<sup>th</sup> day. In contrary, patients with Gram (+) bacterial growth ( $p=0.003$ ), receiving antibiotic regimen involving piperacillin and tazobactam ( $p=0.044$ ) and having empirical antibiotic treatment for at least 72 hours ( $p < 0.001$ ) were more likely to display a more favorable prognosis on the 7<sup>th</sup> day.

Our results indicated that patients with absolute neutrophil count  $< 100/\text{mm}^3$  ( $p=0.002$ ), duration of neutropenia longer than 7 days ( $p=0.001$ ), pneumonia

**Table 1** - Baseline descriptive and clinical data of our series.

Variable	n (%)
<i>Diagnosis</i>	
Acute myeloid leukemia	92 (54.1)
Acute lymphocytic leukemia	23 (13.5)
Myelodysplastic syndrome	11 (6.5)
Chronic myeloid leukemia	2 (1.2)
Chronic lymphocytic leukemia	3 (1.8)
Multiple myelomas	4 (2.4)
Hodgkin lymphoma	8 (4.7)
Non-Hodgkin lymphoma	21 (12.4)
<i>State of disease</i>	
New diagnosis	68 (41.5)
Remission/consolidation	72 (43.9)
Relapse/refractory	24 (14.6)
<i>Duration of hospitalization until detection of febrile neutropenia (days)</i>	
<7	50 (30.5)
7-14	49 (29.9)
>14	65 (39.6)
<i>Febrile neutropenia at admission</i>	
No	144 (87.8)
Yes	20 (12.2)
<i>Comorbidity</i>	
COPD	8 (4.9)
DM	11 (6.7)
CRF	5 (3.0)
CHF	4 (2.4)
Total	34 (20.7)
Absolute neutrophil count < 100/ mm <sup>3</sup>	121 (73.8)
<i>Duration of neutropenia (days)</i>	
<7	101 (61.6)
7-14	35 (21.3)
>14	28 (17.1)
<i>Focus of infection</i>	
Primary bacteremia	80 (48.8)
Pneumonia	39 (23.8)
Urinary tract infection	7 (4.3)
Catheterization	12 (7.3)
Gastrointestinal system	8 (4.9)
Skin	18 (11.0)
Mucositis	28 (17.1)
Central catheterization	48 (29.3)
COPD - chronic obstructive pulmonary disease, DM - diabetes mellitus, CRF - chronic renal failure, CHF - congestive heart failure	

or gastrointestinal foci of infection ( $p<0.001$ ), central catheterization ( $p=0.004$ ), isolation of *Gram* (-) bacteria in culture ( $p=0.005$ ), carbapenem resistance ( $p<0.001$ ), septic shock ( $p<0.001$ ), and bacterial growth during intravenous administration of antibiotic treatment ( $p<0.001$ ) were under more risk for mortality on 21<sup>st</sup> day. In contrary, patients with *Gram* (+) bacterial growth ( $p=0.005$ ), receiving antibiotic regimen involving piperacillin and tazobactam ( $p=0.009$ ) and

having empirical antibiotic treatment for at least 72 hours ( $p<0.001$ ) were more likely to display a more favorable prognosis on the 21<sup>st</sup> day. On the other hand, type of bacteria isolated in cultures seemed not to have a significant impact on the rate of mortality on neither the 7<sup>th</sup> nor the 21<sup>st</sup> day ( $p=0.151$  and  $p=0.127$ ).

Parameters found to be statistically significant in the univariate analyses that were evaluated in a multivariate logistic regression to predict the risk of mortality. The final multivariate logistic regression results showed that pneumonia ( $p<0.0001$ , odds ratio (OR)=0.119, 95% confidence interval(CI)=0.043-0.330), septic shock ( $p=0.004$ , OR=0.185, 95% CI=0.059-0.579) and isolation of *Gram-negative* bacteria ( $p=0.032$ , OR=0.120, 95% CI=0.017-0.836) were statistically significant risk factors for mortality on the 7<sup>th</sup> day. Pneumonia ( $p<0.0001$ , OR=0.040, 95% CI=0.011-0.143) and septic shock ( $p<0.0001$ , OR=0.031, 95% CI=0.006-0.159) were statistically significant risk factors for mortality on the 21<sup>st</sup> day.

**Discussion.** In cancer patients, susceptibility to infections increases due to the disease itself or chemotherapies applied. In neutropenic patients because of decreased inflammatory response, classical findings of infections may not be seen. The first and almost the only indicator of infection is fever. Cases with FEN have higher rates of mortality. Therefore, in the presence of fever in patients with neutropenia, empirical antibiotherapy should be started immediately. Pathogen microorganisms consist mostly of bacteria especially in the early period of infection in patients with FEN. Beside that, most of the deaths from infections in patients with FEN are related to bacteria. Outcomes of autopsy studies have suggested infection-related death rates in patients with acute leukemia and solid tumors are 50-80% and 50%.<sup>10</sup> In the improved management of FEN process, as an important issue, each center should determine its own empirical antibiotherapy protocol. In the determination of empirical antibiotherapy protocol, as an important point, each center should frequently know to isolate pathogen microorganisms at its institute and specify their antimicrobial susceptibility profiles. In this study, one of our objectives was to identify and determine the frequency of pathogen microorganisms isolated during episodes of FEN in acute myeloid leukemia patients followed up. Bacteremia is the most important proof of infection which can be documented in nearly 25% of neutropenic episodes. However, in various studies rates of bacteremia have been reported to change between 11-38% during febrile episodes of neutropenia.<sup>11</sup>

**Table 2 -** Microbiological results and antibiotic sensitivity in our series.

Variable	n (%)
<i>Isolation of resistant bacteria in cultures in the preceding 3 months</i>	
No	156 (95.1)
Yes	8 (4.9)
<i>Type of bacteria isolated in culture</i>	
Gram (+)	34 (20)
Gram (-)	136 (80)
<i>Bacteria isolated in culture</i>	
<i>Pseudomonas aeruginosa</i>	26 (15.3)
<i>Escherichia coli</i>	52 (30.6)
<i>Klebsiella pneumonia</i>	30 (17.6)
<i>Acinetobacter baumannii</i>	17 (10.0)
<i>Enterobacter cloacae</i>	5 (2.9)
<i>Staphylococcus aureus</i>	14 (8.2)
Coagulase (-) staphylococci	8 (4.7)
Enterococci	9 (5.3)
<i>Stenotrophomonas maltophilia</i>	2 (1.2)
<i>Morganella morganii</i>	1 (0.6)
<i>Proteus mirabilis</i>	1 (0.6)
<i>Aeromonas caviae</i>	1 (0.6)
<i>Streptococcus bovis</i>	1 (0.6)
Pneumococci	2 (1.2)
<i>Citrobacter freundii</i>	1 (0.6)
Ceftazidim sensitivity	78 (58.6)
Cefepim sensitivity	88 (66.7)
Piperacillin-tazobactam sensitivity	80 (59.7)
Meropenem sensitivity	108 (80.6)
Imipenem sensitivity	106 (79.1)
Colistin sensitivity	129 (97.7)
ESBL (+) <i>Enterobacteriaceae</i>	35 (20.6)
Carbapenem sensitivity	143 (84.1)
Ciprofloxacin sensitivity	68 (48.9)
Amikacin sensitivity	114 (85.7)
Gentamycin sensitivity	85 (61.6)
Vancomycin-resistant enterococci	3 (1.8%)
Methicillin-resistant staphylococcus aureus	1 (0.6)
Methicillin-resistant coagulase (-) staphylococcus aureus	4 (2.4)
ESBL - extended spectrum beta-lactamase.	

In patients with FEN, mortality rates before empirical antibiotherapy were around 75%; nowadays they have dropped down to 5-10% due to an increase in diagnostic and treatment modalities and the development of standard approaches.<sup>12</sup>

In the empirical treatment of FEN patients, for years, a combination of a beta-lactam and an aminoglycoside antibiotic has been recommended. Various formulated guidelines, in case of initiating empirical antibiotherapy in a group of patients with FEN, recommend a combination of an anti-pseudomonal beta-lactam (penicillin, cefepime, ceftazidime or carbapenem) and

an aminoglycoside antibiotic in consideration of Gram-negative infections and especially *Pseudomonas spp.* infections with higher mortality rates.<sup>6-8</sup> After initiation of patients' treatment, their clinical follow-up and daily physical examinations should be performed excellently, and in case of unresponsiveness to empirical treatment, appropriate modifications should be performed in an attempt to increase the success rate of empirical treatment.<sup>5,6,13</sup> In studies performed recently, in addition to combined treatment regimens, treatment regimens applied using monotherapy with antipseudomonal beta-lactams have been revived.<sup>14,15</sup> In our study, we applied a combination antibiotherapy consisting of a beta-lactam and an aminoglycoside.

In a previous publication, cefepime was combined with amikacin and fever was reportedly controlled in 47.5% of the cases.<sup>16</sup> Serefhanoglu et al,<sup>17</sup> performed a study on 60 cases with hematologic malignancies, and a 30% response rate was achieved in 30 of 89 FEN episodes using piperacillin/tazobactam plus amikacin combination, and with modification, this response rate increased to 63.3%. Rossini et al,<sup>18</sup> achieved a 52.9% success rate in 121 of 252 FEN episodes in patients with hematologic malignancies.

According to data derived from "Infectious Diseases Society of America (IDSA)" and "European Organization for Research and Treatment of Cancer (EORTC), during 1970s Gram-negative bacteria was frequently isolated, while during 1990s Gram-positive bacteria ranked on top with high rates of 60-70%.<sup>3-5,7</sup> But we found that Gram-negative bacteria was the most frequent microorganisms and these data are consistent with the recently reported shift of prevalence from Gram-positive to Gram-negative bacteria in neutropenic patients malignancy.<sup>1,2,11</sup> Endogenous flora that contains mainly of enterobacteriaceae in the gastrointestinal tract can cause bacteremia episodes in patients with neutropenia due to a breakdown of mucosal barriers secondary to chemotherapy.<sup>19</sup> The reduction in the use of the central venous catheter and the reduced presence of severe mucositis may have contributed to a decreasing in Gram-positive bacteremia. In addition, isolation of Gram (+) or Gram (-) bacteria from culture studies seemed to exert a significant impact on the rate of mortality in FEN patients with hematological malignancies.

We found isolation of *Gram-negative* bacteria were statistically significant for mortality on the 7<sup>th</sup> day. But ESBL (+) enterobacteriaceae and carbapenem resistance were not significant in multivariable analysis. Prior studies have revealed that Gram-negative bacteremia in patients with neutropenic fever is usually associated with higher mortality rates than Gram-positive bacteremia.

**Table 3 -** Analysis of the relationship between mortality and clinical/laboratory parameters under investigation.

Variables	Mortality on the 7 <sup>th</sup> day			The prognosis on the 21 <sup>st</sup> day		
	Survival n (%)	Mortality n (%)	P-value	Survival n (%)	Mortality n (%)	P-value
<i>State of disease</i>						
New diagnosis	48 (70.6)	20 (29.4)	0.464	39 (57.4)	29 (42.6)	0.179
Remission/consolidation	57 (79.2)	15/ (20.8)		52 (72.2)	20 (27.8)	
Relapse/refractory	17 (70.8)	7 (29.2)		15 (62.5)	9 (37.5)	
<i>Gender</i>						
Male	67 (71.3)	27 (28.7)	0.290	57 (60.6)	37 (39.4)	0.215
Female	55 (78.6)	15 (21.4)		49 (70)	21 (30)	
<i>Age</i>						
<60	68 (73.1)	25 (26.9)	0.669	58 (62.4)	35 (37.6)	0.487
≥60	54 (76.1)	17 (23.9)		48 (67.6)	23 (32.4)	
Comorbidity	27 (79.4)	7 (20.6)	0.451	26 (76.5)	8 (23.5)	0.105
Absolute neutrophil count <100/mm <sup>3</sup>	84 (69.4)	37 (30.6)	0.014	70 (57.9)	51 (42.1)	0.002
<i>Duration of neutropenia (days)</i>						
<7	84 (83.2)	17 (16.8)	0.003	76 (75.2)	25 (24.8)	0.001
7-14	23 (65.7)	12 (34.3)		19 (54.3)	16 (45.7)	
>14	15 (53.6)	13 (46.4)		11 (39.3)	17 (60.7)	
<i>Focus of infection</i>						
Primary bacteremia	70 (87.5)	10 (12.5)	<0.001	66 (82.5)	14 (17.5)	<0.001
Pneumonia	17 (43.6)	22 (56.4)		10 (25.6)	29 (74.4)	
Urinary tract infection	7 (100)	0/7		7 (100)	0/7	
Catheterization	9 (75)	3 (25)		6 (50)	6 (50)	
Gastrointestinal system	5 (62.5)	3 (37.5)		5 (62.5)	3 (37.5)	
Skin	14 (77.8)	4 (22.2)	12 (66.7)	6 (33.3)		
Mucositis	21 (75)	7 (25)	0.935	17 (60.7)	11 (39.3)	0.634
Central catheterization	30 (62.5)	18 (37.5)	0.025	23 (47.9)	25 (52.1)	0.004
Isolation of Gram (+) bacteria in culture	32 (94.1)	2/34 (5.9)	0.003	29 (85.3)	5/34 (14.7)	0.005
Isolation of Gram (-) bacteria in culture	94 (69.1)	42 (30.9)	0.003	81 (59.6)	55 (40.4)	0.005
ESBL (+) Enterobacteriaceae	104 (77.0)	31 (23.0)	0.088	93 (68.9)	42/135 (31.1)	0.025
Carbapenem resistance	11 (40.7)	16 (59.3)	<0.001	7 (25.9)	20 (74.1)	<0.001
Polymicrobial bacteremia	119 (74.8)	40 (25.2)	0.839	103 (64.8)	56 (35.2)	0.718
<i>Empirical antibiotic regimen</i>						
Piperacillin-tazobactam	101 (78.9)	27 (21.1)	0.044	90 (70.3)	38 (29.7)	0.009
Imipenem	11 (57.9)	8 (42.1)		10 (52.6)	9 (47.4)	
Meropenem	10 (58.8)	7 (41.2)		6 (35.3)	11 (64.7)	
Bacterial growth during antibiotic treatment	9 (40.9)	13 (59.1)	<0.001	8 (26.7)	22 (73.3)	<0.001
Administration of appropriate antibiotic treatment for minimum 72 hours	119 (86.2)	19 (13.8)	<0.001	104 (75.4)	34 (24.6)	<0.001
Septic shock	9 (40.9)	13 (59.1)	<0.001	3 (13.6)	19 (86.4)	<0.001

ESBL - extended spectrum beta-lactamase

But the influence of bacteremia due to Gram-negative bacteria with and without antibiotic resistance on outcomes of hematological patients is controversially. Some authors reported a worse outcome of multidrug-resistant bacteremia due to Gram-negative bacteria compared to susceptible Gram-negative bacteria bloodstream infections<sup>20,21</sup> Whereas others could not.<sup>22,23</sup> We think that surveillance studies to monitor the rates of antibacterial resistance are important. According to the results of our study, we think that

initiation of effective empirical antibiotic treatment without delay as well as controlling the severity and duration of neutropenia may significantly improve the results of treatment in FEN patients with hematological malignancies. Furthermore, selection of antibiotic protocol must be tailored with special conditions and experience in every center.

Apart from the different empirical antibiotherapy regimens selected for initial treatment of neutropenic patients, the most important factors which predict the

prognosis of various infections are the progression of the underlying disease, whether it is kept under control or not and potential improvement of neutropenia. Therefore the underlying diseases of the patients should be treated appropriately, the presence of fever and infection should not be seen as a factor which delays treatment of primary disease.<sup>9</sup>

We found pneumonia and septic shock were important factors associated with mortality. In this patient group, clinical and laboratory findings which reflect the severity of infection and aid in the early diagnosis. The underlying disease should be attentively reviewed to discriminate between febrile episodes with low and high-risk FEN episodes, to predict septic complications.

Some limitations of the current study must be remembered during extrapolation of our results to larger populations. These include retrospective design, data limited to the experience of a single institution and impact of social, genetic and environmental factors.

In conclusion, early diagnosis and appropriate treatment of serious infections which are important causes of morbidity and mortality in neutropenic patients are quite important. However, an inadequate number of clinical and microbiological data in these patients pose great problems in the diagnostic approach. Because of these indications, treatment of FEN patients with broad-spectrum antibiotherapy has been a standard approach. However, as it is known, this approach leads to problematic issues in the development of resistance, secondary infection, increase in expenses and toxicity. Each center should closely follow-up its own causes of infection, determine its empirical antibiotherapy policies which may contribute favorably to the more improved management of FEN process.

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## References

- Tohamy ST, Aboshanab KM, El-Mahallawy HA, El-Ansary MR, Afifi SS. Prevalence of multidrug-resistant Gram-negative pathogens isolated from febrile neutropenic cancer patients with bloodstream infections in Egypt and new synergistic antibiotic combinations. *Infect Drug Resist* 2018; 11: 791-803.
- Forcina A, Lorentino F, Marasco V, Oltolini C, Marcatti M, Greco R, et al. Clinical Impact of Pretransplant Multidrug-Resistant Gram-Negative Colonization in Autologous and Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant* 2018; 24: 1476-1482.
- Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; 34: 730-751.
- Infectious Diseases Society of Taiwan; Hematology Society of Taiwan; Medical Foundation in Memory Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccine. Guidelines for the use of antimicrobial agents in patients with febrile neutropenia in Taiwan. *J Microbiol Immunol Infect* 2005; 38: 455-457.
- Akova M, Paesmans M, Calandra T, Viscoli C; International Antimicrobial Therapy Group of the European Organization for Research and Treatment of Cancer. A European Organization for Research and Treatment of Cancer-International Antimicrobial Therapy Group Study of secondary infections in febrile, neutropenic patients with cancer. *Clin Infect Dis* 2005; 40: 239-245.
- Jarque I, Salavert M, Sanz MA. [Management of febrile neutropenic patients]. *Enferm Infecc Microbiol Clin* 2005; 23: 24-29. Spanish
- Sharma A, Lokeshwar N. Febrile neutropenia in haematological malignancies. *J Postgrad Med* 2005; 51: S42-S48.
- Tamura K. Clinical guidelines for the management of neutropenic patients with unexplained fever in Japan: validation by the Japan Febrile Neutropenia Study Group. *Int J Antimicrob Agents* 2005; 26: S123-S127; discussion S133-S140.
- Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med* 1993; 328: 1323-1332.
- Viscoli C. The evolution of the empirical management of fever and neutropenia in cancer patients. *J Antimicrob Chemother* 1998; 41: 65-80.
- Trecarichi EM, Pagano L, Candoni A, Pastore D, Cattaneo C, Fanci R, et al. Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. *Clin Microbiol Infect* 2015; 21: 337-343.
- Young SD, Feld R. Fever associated with chemotherapy-induced neutropenia: a review of current therapeutic approaches. *Curr Opin Infect Dis* 1998; 11: 401-409.
- D'Antonio D, Staniscia T, Piccolomini R, Fioritoni G, Rotolo S, Parruti G, et al. Addition of teicoplanin or vancomycin for the treatment of documented bacteremia due to gram-positive cocci in neutropenic patients with hematological malignancies: microbiological, clinical and economic evaluation. *Chemotherapy* 2004; 50: 81-87.
- Maschmeyer G, Haas A. The epidemiology and treatment of infections in cancer patients. *Int J Antimicrob Agents* 2008; 31: 193-197.
- Sipsas NV, Bodey GP, Kontoyiannis DP. Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. *Cancer* 2005; 103: 1103-1113.
- Tamura K, Imajo K, Akiyama N, Suzuki K, Urabe A, Ohyashiki K, et al. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. *Clin Infect Dis* 2004; 39: S15-S24.
- Serephanoglu K, Ersoy Y, Serephanoglu S, Aydogdu I, Kuku I, Kaya E. Clinical experience with three combination regimens for the treatment of high-risk febrile neutropenia. *Ann Acad Med Singapore* 2006; 35: 11-16.
- Rossini F, Terruzzi E, Verga L, Larocca A, Marinoni S, Miccolis I, et al. A randomized clinical trial of ceftriaxone and amikacin versus piperacillin tazobactam and amikacin in febrile patients with hematological neoplasia and severe neutropenia. *Support Care Cancer* 2005; 13: 387-392.

19. Gedik H, Simşek F, Kantürk A, Yildirmak T, Arica D, Aydin D, et al. Bloodstream infections in patients with hematological malignancies: which is more fatal - cancer or resistant pathogens? *Ther Clin Risk Manag* 2014; 10: 743-752.
20. Kang CI, Chung DR, Ko KS, Peck KR, Song JH; Korean Network for Study of Infectious Diseases. Risk factors for infection and treatment outcome of extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with hematologic malignancy. *Ann Hematol* 2012; 91: 115-121.
21. Cornejo-Juárez P, Vilar-Compte D, Pérez-Jiménez C, Ñamendys-Silva SA, Sandoval-Hernández S, Volkow-Fernández P. The impact of hospital-acquired infections with multidrug-resistant bacteria in an oncology intensive care unit. *Int J Infect Dis* 2015; 31: 31-34.
22. Kim SH, Kwon JC, Choi SM, Lee DG, Park SH, Choi JH, et al. *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with neutropenic fever: factors associated with extended-spectrum  $\beta$ -lactamase production and its impact on outcome. *Ann Hematol* 2013; 92: 533-541.
23. Ha YE, Kang CI, Cha MK, Park SY, Wi YM, Chung DR, et al. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* in patients with cancer. *Int J Antimicrob Agents* 2013; 42: 403-409.

## Statistics

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Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.