Original Article

Evaluation of febrile neutropenic attacks in a tertiary care medical center in Turkey

Suzan Sacar[1], Sibel Kabukcu Hacioglu[2], Ali Keskin[2], Huseyin Turgut[1]

[1]*Department of Clinical Microbiology and Infectious Diseases, Pamukkale University Faculty of Medicine, Kinikli, Denizli, Turkey*
[2]*Department of Internal Medicine, Pamukkale University Faculty of Medicine, Kinikli, Denizli, Turkey*

Abstract

Background: Infectious complications in febrile neutropenic patients are still major causes of morbidity and mortality despite significant advances in diagnostic techniques and antimicrobial therapy. In this study, we describe the characteristics of patients with hematological malignancies who were evaluated for suspected infection. This study was also conducted to assess the isolation rate of bacterial and fungal causative agents in febrile neutropenic attacks.

Method: The study was conducted at Pamukkale University Hospital, Turkey. In order to identify the characteristics of patients with hematological malignancies in the presence/suspicion of any accompanying infectious disease, patients' charts with hematological malignancies were reviewed for signs/symptoms of any infection between October 1, 2001, and May 31, 2005, retrospectively.

Results: Overall, 90 infectious episodes occurred in 59 patients. The most common underlying diseases were acute myelogenous leukemia (61.0%) and acute lymphocytic leukemia (15.3%). The absolute neutrophil count was lower than 100/mm³ in 33 (36.7%) episodes. Microbiologically and clinically documented infections and fever of unknown origin were observed in 35.6%, 28.9%, and 35.6% of the participants, respectively. Bloodstream infections and pneumonia were detected in 21.1% and 18.9% of episodes, respectively. Gram negative organisms were most common (58.4%), followed by gram positive cocci. A combination of third generation cephalosporin and an aminoglycoside were used in 44.4% of episodes initially. Fever resolved in 24.4% of episodes using the initial therapy. The mortality rate was 15.6%.

Conclusion: These results showed that infections with gram-negative bacteria continue to predominate in febrile neutopenic episodes in our center.

Key Words: hematology, fever, bacteremia, neutropenia.

J Infect Developing Countries 2008; 2(5):359-363.

Received 19 December 2007 - Accepted 5 August 2008

Introduction

Infectious complications in febrile neutropenic patients are still major causes of morbidity and mortality despite significant advances in diagnostic techniques and antimicrobial therapy. Frequently, the bacterial aetiology is unknown at the onset of infection [1,2]. There were major changes in the type and range of pathogens causing infection in neutropenic patients during the last decades. Gram-negative bacteria were more prevalent before the mid-1980s. However, Gram-positive cocci, generally considered to be less virulent, especially coagulase negative staphylococci, have become increasingly common since the mid 1980s. But since the begginning of the new century, Gram-negative bacilli have re-emerged [3,4].

The clinician must have knowledge of the prevalence of causative bacteria in neutropenic patients with fever and their antibiotic susceptibilities in the local area in order to choose the proper antibiotic. In this study, we describe the characteristics of neutropenic patients with hematological malignancies who were evaluated for suspected infection. The study was also conducted to assess the isolation rate of bacterial and fungal causative agents in febrile neutropenic attacks.

Materials and Methods

The study was conducted at Pamukkale University Hospital**,** Denizli, Turkey**.** In order to identify the characteristics of patients with hematological malignancies in the presence/suspicion of any accompanying infectious disease, patients with hematological malignancies evaluated for signs/symptoms of any infection between October 1, 2001, and May 31, 2005, were retrospectively reviewed.

Patients were eligible if they had a single measurement of oral temperature 38.5° or 38.0°C on two or more occasions within 12 hours, and the fever was not related to the administration of blood products or known pyrogenic substances [5]. All patients were evaluated by thorough physical examination. Blood cultures were taken from a central or a peripheral vein before antibiotic initiation and every 24 hours thereafter during persistent fever until culture results became negative. Bacterial blood-stream infection was defined as the presence of clinical symptoms in association with one, of a set of two, positive cultures when the isolated pathogen was a gram-negative agent or associated with two or more positive blood cultures when the pathogen isolated was a gram-positive agent. When fungal species were isolated from one or more blood cultures, it was accepted as fungal blood-stream infection [6]. Additionally, cultures from urine samples and, if appropriate, from other suspected body sites were obtained. All patients were evaluated by a complete blood count and urine analysis, and standard blood chemistry.

A febrile episode was determined as a microbiologically documented infection when bloodstream infection was verified or cultures showed growth from a site of infection; a clinically documented infection when a suspected site of infection was identified without microbiological confirmation; and a fever of unknown origin when no site was identified and no microbiological evidence of infection was found. All organisms isolated from clinical specimens were identified by standard criteria in our clinical microbiology laboratory [7].

Patients were given empirical antibiotic therapy when a febrile neutropenic episode was defined while awaiting the culture results. In patients with microbiologically documented infection, treatment was modified according to the isolated pathogen and its susceptibility. A treatment modification was not done before 72 hours unless a resistant microorganism was cultured during that period or the patient's condition notably deteriorated.

Statistical analysis

All data are described as mean ± SD. Continuous variables were compared using the independent-samples *t* test and categorical variables were compared using the chi-square test or Fisher's exact test for association. Differences were considered statistically significant when $P < 0.05$. Data were analyzed by statistical software (SPSS for Windows 11.0; SPSS, Chicago, Illinois).

Results

Overall, 90 infectious episodes occurred in 59 patients. Table 1 summarises the demographic data for the patients with febrile neutropenic attacks included in the study. The absolute neutrophil count (ANC) was between 500 and 1000/mm^3 in 27 (30%) episodes, between 100 and 500/mm^3 in 30 (33.3%) episodes and lower than 100/mm³ in 33 (36.7%) episodes. In the patients with bloodstream infection, the ratio of ANC below 100/mm^3 and between 100 and 500/mm3 was 52.6% (10) and 47.4% (9), respectively. The mean count of cultures was 9.2±6.8 (3-29).

Table 1. Demographic data for 59 patients with febrile neutropenic attacks.

Variable	Febrile neutropenic patients
Age (yr; mean±SD; range)	48.3+18.9 (18-80)
Gender (Male) N (%)	76.3%
Underlying disease; n (%)	
Acute myelogenous leukemia	61.0%
Acute lymphocytic leukemia	15.3%
Non-Hodgkin's lymphoma	5.1%
Idiopatic neutropenia	5.1%
Others (aplastic anemia, chronic granulocytic leukomia, and hairy-cell leukemia, etc)	13.5%
Mean duration of fever (day; mean±SD; range)	11±7.3 (2-42)
Mean duration of antibiotic treatment (day; mean ± SD; range)	15.6±7.6 (5-46)
Death	14 (15.6%)

Microbiologically and clinically documented infections and fever of unknown origin were observed in 35.6%, 28.9%, and 35.5% of the participants, respectively. Blood-stream infections and pneumonia were detected in 19 episodes (21.1%) and 17 episodes (18.9%), respectively. In 56.3% of culture-proven episodes (18 cases), blood-stream infection was considered the cause of fever, followed by pneumonia in 15.6% (five cases), and by urinary tract infections in 12.5% (4 events) (Table 2). A single pathogen was isolated in 28 of the culture positive episodes and two patogens in four. Microbiologically, gram negative organisms (58.4%) (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia*) were most common, followed by gram positive (*Staphylococcus epidermidis, S. aureus*) (Table 3). There were three ESBL producing gram-negative bacilli (two *E. coli* and one *K. pneumoniae*). Susceptibility patterns in gram-negative isolates are given in Table 4. Resistance to oxacillin was detected in three (75%) of *S. aureus* and two (28.6%) of *S. epidermidis*. No glycopeptide-resistant

gram-positive isolates were isolated. None of the streptococcal isolates was penicillin resistant. The ratio of gram-positive and gram-negative microorganisms causing blood-stream infections was equal (50%). *E. coli* (five isolates; 27.8%) was the predominant microorganism isolated from bloodstream infections, followed by methicillin-sensitive *S. epidermidis* (four isolates; 22.2%) and methicilline resistant *S. aureus* (three isolates; 16.7%) (Table 5). One of the *E. coli* strains isolated from the subsequent episodes was ESBL, while no ESBL strain was isolated from the initial episodes. Similarly, resistance to oxacillin among the isolated staphylococci from blood was determined to be higher in the subsequent episodes in comparison with the initial ones. During the study there was neither an outbreak nor a cluster of cases due to a specific microorganism.

Table 2. Infectious complications identified during the study period.

Type of infection	Number	%
Microbiologically documented infections	**32**	**35.6**
Blood stream infections	18	56.3
Pneumonia	5	15.6
Urinary tract infections	4	12.5
Gastrointestinal tract infections	3	9.4
Skin, soft tissue infections	1	3.1
Central nervous system infections	1	3.1
Fever of unknown origin	**32**	**35.5**
Clinically documented infections	**26**	**28.9**
Pneumonia	12	46.2
Skin, soft tissue infections	4	15.4
Urinary tract infections	4	15.4
Gastrointestinal tract infections	3	11.5
Perianal infections	2	7.7
Blood stream infections	1	3.8
Total	**90**	**100**

Table 3. Pathogens isolated in febrile neutropenic attacks.

Microorganism	Number	%
Gram-negative bacilli	**21**	**58.4**
Escherichia coli	9	25
Klebsiella pneumonia	4	11.1
Pseudomonas aeruginosa	4	11.1
Enterobacter spp.	2	5.6
Acinetobacter spp.	2	5.6
Gram-positive bacteria	**13**	**36.1**
MSSE	5	13.9
MRSA	3	8.3
MRSE	2	5.6
Streptococcus viridans	2	5.6
MSSA	1	2.8
Fungi	**2**	**5.6**
Candida albicans	1	2.8
Non-albicans candida	1	2.8
Total	**36**	**100**

MSSE=Methicilline sensitive *S. epidermidis*, MRSA: Methicillin resistant *S. aureus*, *MRSE*=Methicillin resistant *S. epidermidis*, *MSSA*= Methicillin sensitive *S. aureus.*

The most commonly used initial therapies were a combination of third generation cephalosporin and an aminoglycoside (44.4%), antipseudomonal betalactam-betalactamase inhibitors (12.2%) and carbapenems (11.1%). Fever resolved in 24.4% of episodes using the initial therapy; in the remainder, second-line antibiotics (mainly glycopeptyde) and antifungals (amphotericin-B) were added empirically or depending on culture and sensitivity. Antibiotics were discontinued when initial blood cultures had no growth after at least 48 hours and no source of infection was found, the blood count was improving, and if the patient became afebrile and clinically well. A total of 14 patients (15.6%) died during the infectious episode. Gram-positive microorganisms were found in five patients (35.7%), while gram-negative microorrgansims were isolated from four patients (28.6%).

Table 4. Susceptibility patterns in Gram-negative bacilli (percentage of resistance to tested antibiotics).

Bacteria	AK	AMP	CTX	CEFT	CRP	IMP	TMP
Escherichia coli	11	100	22	22	33	0	89
Klebsiella pneumonia	0	50	25	25	0	0	100
Pseudomonas aeruginosa	25	100	100	50	50	0	100
Enterobacter spp.	50	100	50	50	0	0	100
Acinetobacter spp.	50	100	100	100	0	0	100

AK = amikacin; AMP = ampicillin; CTX = cefotaxime; CEFT = ceftazidime; CRP = ciprofloxacin; IMP = imipenem; TMP = trimethoprim-sulfamethoxasole.

Table 5. Microorganisms isolated from the patients with blood stream infection.

Microorganism	Initial episode (n)	Subsequent episodes (n)	Total N	Total %
Gram-negative bacilli	**4**	**5**	**9**	**50**
Esherichia coli	2	3	5	27.7
Acinetobacter spp.	1	1	2	11.1
Klebsiella pneumonia	1	0	1	5.6
Pseudomonas aeruginosa	0	1	1	5.6
Gram-positive bacteria	**3**	**6**	**9**	**50**
Methicilline sensitive *S. epidermidis*	2	2	4	22.2
Methicillin resistant *S. aureus*	1	2	3	16.6
Methicillin resistant *S. epidermidis*	0	1	1	5.6
Streptococcus viridans	0	1	1	5.6
Total	**7**	**11**	**18**	**100**

There was no statistically important difference between the deaths due to gram-positive and negative microorganisms (P>0.05). The death ratio in the patient group with blood-stream infection was 26.3%, whereas in the group without blood-stream infection the death ratio was 12.7%. There was no statistically important difference between the groups in accordance to death ratio (P>0.05).

Discussion

Febrile neutropenia is a potentially life-threatening situation, as severe infections are common, requiring prompt medical intervention [8-10]. Identification of the

causative microorganisms of infection is possible in only 22% to 39% of cases [2,9].

According to the recent reports, gram-negative bacilli have re-emerged as the dominant pathogens in febrile neutropenic patients in some European centres. On the other hand, data from the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) Project reports that gram-positive cocci still predominate in the USA [11-13].

Gram negative bacilli were the most commonly isolated microorganisms in our study, followed by gram positive cocci. Although the ratio of causative gram-positive and gram-negative agents of blood-stream infection was equal, *E. coli* was the predominant one (27.8%). The possible reason that gram-negative baciili are predominant in our neutropenic patients is that we do not use flouroquinolones and cotrimoxasole as prophilactic agents and catheters are used only as required.

Analysis of data from Turkey over an 18-year period showed that the Gram-negative bacilli were the dominant isolates with a ratio of 52% (243/468), but they accounted for only 41.5% of bloodstream infections [14]. On the other hand, a multicenter study from our country reported that 79% of all bacteraemic episodes (11 of 14) were caused by Gram-positive bacteria [15]. As it is obviously seen, there are significant differences in the epidemilogical profiles among the areas in our country. Recent studies from other developing countries also report different results [16,17].

Additionally, an increasing frequency of infections caused by fungi and an increased mortality due to them has been reported [18]. However, only two fungal infections were detected in our study. The incidance of streptococcal infections in cancer patients has also been rising for the past years and the viridans streptococci have now become one of the frequently organisms from blood-stream infection in neutropenic patients [19]. Streptococcus viridans accounted for 5.6% of isolated microorganisms from all patients in our study. The ratio of this pathogen was the same for the blood-stream infection.

In the present study, blood-stream infection was found to be the most common infection in our febrile neutropenic patients. Sigurdardottir *et al*. found that the ratio of gram-negative and gram-positive bacteria among the isolated pathogens from the patients with blood-stream infections was 49.2% and 45.9%, respectively [20]. As in our study, the most frequent isolated bacteri was *E. coli* (%25.4). On the other hand, Gaytan-Martinez *et al*. also found blood-stream infection to be the predominant infection in their febrile neutropenic patients, but it was due mainly to gram-positive cocci [6].

In the present study, infection was microbiologically or clinically documented in 58 episodes (64.5%). In a multicenter study reported from our country, that ratio was 69% [15]. Dikici *et al*. 21 were more successful in the isolation of microorganisims with a ratio of 42.7%. The ratio of fever of unknown origin (36.6%) was similar to ours.

The incidence of infection is demonstrated to be correlated with a granulocyte count of 27 and bacteremia usually develops when neutrophils fall to <100/mm^3 [10,12]. Dikici *et al*. [21] reported that ANC was below 100/mm^3 in 32.9% of the episodes, which is slightly lower than our result. The ratio of ANC below 100/mm3 in the patients with bloodstream infection was 37%, while in our study it was 52.6%. The mean antibiotic usage duration was shorter approximately by five days than the duration found in our study (10.8 ± 5.1 days). A study from our country reported that fever persisted for 1 to 30 days in their neutropenic patients, while this duration in our study was 2 to 42 days [22].
Continious surveillance in local hospitals is also important for the monitoring of rates of resistant organisms. A study of the incidence of ESBL-producing *K. pneumoniae* among febrile neutropenic paediatric patients found that 51.6% of isolates were ESBL producers [23]. The fact that ESBL-producing *E. coli* and *K. pneumonia* were also found in our study should be kept in mind when a patient with persistent fever in our center does not respond to the given therapy.

Our preferred regimen in the initial therapy was the combination of third-generation cephalosporin and an aminoglycoside. The combination of an anti-pseudomonal beta-lactam and an aminoglycoside has been the treatment most frequently used as the initial empirical therapy of suspected infections in febrile neutropenic patients, especially in those with high risk factors for infection [5]. We used this regimen in 12.2% of the patients. Recent studies demonstrated that monotherapy can successfully replace combination therapy in febrile neutropenic patients [25].

Imipenem was observed to be the most efficient antibiotic to gram-negative microorganisms. Similarly, Sigurdardottir *et al*. found that the most efficient antibiotics against the isolated gram negative microorganisms were imipenem and ciprofloxacin [20]. Fever resolved only in 24.4% of episodes using the initial therapy; in the remainder, second-line

antimicrobials had to be added empirically or depending on culture and sensitivity. As is described in the guidelines, glycopeptydes and/or antifungals were added when there was no response to the previous therapy [5,12,24]. A study from our country reported that an antibiotic therapy was modified in more than half of the episodes [26].

The overall mortality rate among our febrile neutropenic patients was 15.6%, while it was as high as 26.3% in the patients with blood-stream infection. Recent studies from our country reported that the mortality rate among febrile neutropenic patients was 11.6% [16,21].

Conclusion

The shift toward gram-positive organisms and the continuing need to provide gram-negative coverage demands the use of an agent or agents that provide coverage for the spectrum of potential infecting organisms. Studies reporting local microbiological findings are necessary for appropriate antibiotic choice. Although the etiology of febrile neutropenic infections has shifted from gram negative to gram positive organisms in many centers, our results show that infections with gram negative bacteria continue to predominate in febrile neutropenic attacks in our center.

References

1. Donowitz GR (1996) Fever in the compromised host. Infect Dis Clin N Am 10:129-148.
2. De Pauw BE, Verweij PE: Infections in patients with hematologic malicnancies. Principles and Practice of Infectious Diseases. Mandell GL, Bennett JE, Dolin R (eds) 2005 Philadelphia, Pennsylvania, Elsevier Churchill-Livingstone, 6th Ed, pp 3432-3441.
3. Akova M (2006) Emerging problem pathogens: A review of resistance patterns over time Int J Infect Dis 10:S3–S8.
4. Glauser MP, Pizzo PA (2000) Management of infections in immunocompromised patients. London, New York: WB Saunders.
5. Hughes WT *et al*. (2002) Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis 34: 730-751.
6. Martinez-Gaytan J *et al*. (2000) Microbiological findings in febrile neutropenia. Arch Med Res 31: 388-392.
7. Jorgensen JH *et al*. (1997) National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Test Approved Standard. 6th edition NCCLS, Pennsylvania, 17(1): M2-A6.
8. Schimpff SC (1985) Overview of empiric antibiotic therapy for the febrile neutropenic patient. Rev Infect Dis 7: S734–740.
9. De Lalla F (1997) Antibiotic treatment of febrile episodes in neutropenic cancer patients. Drugs 53: 789-804.
10. Hughes WT *et al*. (1990) From the Infectious Diseases Society of America. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis161: 381-396.
11. Hann I, Viscoli C, Paesmans M (1997) A comparison of outcome from febrile neutropenic episodes in children compared with adults, results from four EORTC trails. Br J Haematol99: 580-588.
12. Pizzo PA (1993) Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 18: 1323-1332.
13. Antoniadou A, Petrikkos G, Toskas A (1995) Secular trends and significance of bacteremias in neutropenic patients in Greece (1986–1994). 19th International Congress of Chemotherapy. Abstract No. 0630, July 16–21, Montréal, Canada.
14. Calik N *et al*. (2005) Epidemiology of bacterial infections and risk factors for mortality in cancer patients. In: Abstracts ICAAC, Washington DC, USA. K-1529.
15. Meropenem Study Group of Turkey, Akova M, Akan H (1999) Comparison of meropenem with amikacin plus ceftazidime in the empirical treatment of febrile neutropenia: a prospective randomised multicentre trial in patients without previous prophylactic antibiotics. Int J Antimicrob Agents 13: 15-19.
16. Volkow P *et al*. (1994) Experinece of an intravenous therapy team at the Instituto Nacional de Cancerologia (Mexico) with a long-lasting, low-cost silastic venous catheter. Clin Infect Dis 18: 719-725.
17. Miranda-Novales MG *et al*. (1998) Empirical antimicrobial therapy in pediatric patients with neutropenia and fever. Risk factors for treatment failure. Arch Med Res 29: 331-335.
18. Denning DW *et al*. (1997) Guidelines fort he investigation of invasive fungal infections in haematological malignancy and solid organ transplantation. Eur J Clin Microbiol Infect Dis16: 424-436.
19. Oppenheim BA (1998) The changing pattern of infection in neutropenic patients. J Antimicrob Chemother 41(D): 7-11.
20. Sigurdardottir K *et al*. (2005) A multi-centre prospective study of febrile neutropenia in Norway: Microbiological findings and antimicrobial susceptibility. Scand J Infect Dis 37: 455-464.
21. Dikici N, Ural O (2002) An evaluation of febrile neutropenic attacks. Flora J Infect Dis Clin Microbiol 7: 185-190.
22. Aksoylar S, Cetingul N, Kantar M (2004) Meropenem plus amikacin versus piperacillin tazobactam plus netilmicin as empiric therapy for high-risk febrile neutropenia in children. Pediatr Hematol Oncol 21: 115-123.
23. Ariffin H *et al*. (2000) Ceftazidime resistant *Klebsiella pneumoniae* bloodstream infection in children with febrile neutropenia. Int J Infect Dis 4: 21-25.
24. Febrile Neutropenia Working Group (2004) Guidelines for Diagnosis and Therapy in febrile neutropenic patients. Flora J Infect Dis Clin Microbiol 9: 5-28.
25. Cometta A *et al*. (1996) Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 40: 1108-1115.
26. Cagatay AA, Punar M, Nalcaci M (2001) Febrile neutropenia agents in patients with hematological malgnancies. J Klimik 14: 7-9.

Corresponding Author: Suzan Sacar, Pamukkale University Faculty of Medicine, Department of Infectious Diseases and Clinical, Microbiology, Kinikli, Denizli, Turkey E-mail: suzansacar@yahoo.com

Conflict of interest: No conflict of interest is declared.