Microorganisms Isolated from Blood Cultures of Febrile Neutropenic Patients in İbn-i Sina Hospital

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ABSTRACT

Patients with profound neutropenia have increased risk of septicemia associated with significant morbidity. To provide the appropriate broad-spectrum antimicrobial cover, documentation of causative agents and their antimicrobial susceptibilities should be established in each hospital. During 2001 in Ibn-i Sina Hospital Hematology unit, among 125 isolates from blood cultures of febrile neutropenic patients, gram-negative bacteria was prevalent (56.8%). Among the gram-positives (34.4% of isolates) coagulase-negative staphylococci (CNS) were the predominant bacteria (15/43) followed by *Staphylococcus aureus* (12/43). *Escherichia coli* (23/71) and *Klebsiella* spp. (15/71) were the most common species among 71 gram-negative bacteria. Nonfermentative gram-negative bacilli were 21.6% of the isolates. Increase in the isolation rate of *Acinetobacter baumannii* (7 strains) and *Stenotrophomonas maltophilia* (6 strains) was noticed.

Key Words: Febrile neutropenia, Bacteremia, *Stenotrophomonas maltophilia*, Gram-negative rod, Nonfermentative.

ÖZET

İbn-i Sina Hastanesi'nde Febril Nötropenik Hastaların Kan Kültürlerinden İzole Edilen Mikroorganizmalar

Nötropenik hastalarda septisemi riski yüksek olup, belirgin morbiditeye sahiptir. Bu hastalarda uygun geniş spektrumlu antibiyotik tedavisi için her hastanede etkenlerin gösterilmesi ve bunların antimikrobiyal duyarlılıklarının belirlenmesi gereklidir. 2001 yılında Ankara Tıp Fakültesi İbn-i Sina Hastanesi'nde febril nötropenik hastalardan elde edilen 125 kan kültürü izolatında gram-negatif bakterilerin ön planda olduğu (%56.8) görüldü. Gram-pozitif izolatlarda (%34.4) ise koagülaz-negatif stafilokoklar hakimken (15/43) bunu *Staphylococcus aureus* izlemekte idi (12/43). Yetmişbir gram-negatif izolatta *Escherichia coli* (23/71) ilk sırada yer alırken *Klebsiella* spp. (15/71) bunu izlemekte idi. İzolatların %21.6'sı nonfermenter gram negatif basildi. *Acinetobacter baumannii* (7 suş) ve *Stenotrophomonas maltophilia* (6 suş)'da artış dikkati çekti.

Anahtar Kelimeler: Febril nötropeni, Bakteremi, *Stenotrophomonas maltophilia*, Nonfermentatif gram-negatif basil.

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INTRODUCTION

Infection remains an important cause of morbidity and mortality in febrile neutropenia and bacteremia is the estimated cause of fever in 25% of all neutropenic patients[1]. Due to high mortality, the agents causing bacteremia and sepsis should be known for therapy and empirical antibiotic use. The etiological agents and their antibiotic susceptibilities differ by time and by hospitals as a result of different therapeutic and medical manipulations and antibiotic polices. As early administration of appropriate antibiotics is crucial for successful management of infections, close and at least yearly monitorization of causative agents is mandatory in each center[2]. In this study the microorganisms isolated from blood cultures of neutropenic patients in Ankara University Ibn-i Sina Hospital hematology unit in 2001 is presented and the results compared with different studies from Turkey.

MATERIALS and METHODS

The selected patients were adults hospitalized in the hematology unit of Ibn-i Sina Hospital, whose blood cultures were obtained at the time they had fever and neutropenia (PMNL < 500/mm^3)[3]. At least one set of blood cultures were taken just before the initiation of antimicrobial therapy and cultures were observed by BACTEC 9240 continuous monitoring system (BD Biosciences). Microbiological investigation of positive cultures (isolation and identification procedures), were done by classical microbiological methods and by miniAPI identification system (Biomerieux). All of the isolates were considered to be significant except commensal skin flora members (coagulase-positive staphylococci, micrococci, *Bacillus* spp., diphteroids and alpha-hemolytic streptococci). For this group, at least two consequent isolates either both from peripheral veins or one from catheter site and one from peripheral vein was the main requirement for positivity. In case of one positive blood culture with an isolate of skin flora members in patients with intravenous indwelling catheters, presence of clinical picture of septicemia was sought for consideration of significant positivity[4,5]. Similar studies from different centers in our country reported in 5th Symposium of Febrile Neutropenia in 2003, are evaluated to compare results from different hospitals. The studies that mentioned the agents of bacteremia are included in the comparison.

RESULTS

During the year 2001, we obtained 125 microorganisms from 121 febrile neutropenic episodes. Seventy-one (56.8%) of the isolates were gram-negative bacteria (Enterobacteriaceae 44, nonfermentatives 27) and (34.4%) were gram-positives (cocci 40, coryneforms 3). The predominant bacteria were *Escherichia coli*, *Klebsiella* spp., and coagulase-negative staphylococci. The lists of isolates are shown in Table 1. There were 5 reports from different hospitals mentioning the agents of bacteremia and/or fungemia in the 5th febrile neutropenia symposium book[6-10]. In two of the reports gram-positives were the main microorganisms with an isolation rate over 70%. In the others the gram-negatives were more common but a small difference in the isolation rate between gram-positives and negatives were observed.

DISCUSSION

The reduction of mortality with the immediate use of empiric antimicrobial therapy while awaiting definitive microbiological data on the infectious origin in febrile neutropenic cancer patients, have been shown for decades ago[11]. The antibiotic choices should depend on microbiological data obtained from such patients. For localized and clinically apparent infections it is easier to take microbiological cultures from infected sites and start antibiotic therapy but many of febrile neutropenic episodes appear only by fever and the only sample in the diagnosis and therapy will be the blood cultures[12]. Approximately 80% of identified infections among neutropenic patients are believed to arise from patients'

Table 1. The types of microorganisms from positive cultures

Bacteria	**n**	**%**		**n**	**%**		**n**	**%**
Gram-positive	43	34.4	**Gram-negative**	71	56.8	***Candida* spp.**	10	8.0
Staphylococcus spp.	27		Enterobacteriaceae	44	35.2	*C. albicans*	6	
S. aureus	12		*E. coli*	23		*C. tropicalis*	3	
CNS -*S. epidermidis*	10		*Klebsiella* spp.	15		*C. glabrata*	1	
-Other CNS	5		*Enterobacter* spp.	4				
Enterococcus spp.	9		*Proteus mirabilis*	1				
Streptococcus spp.	4		*Pantoea* spp.	1				
Group A beta-hemolytic streptococci	1		**Nonfermentatives**	27	21.6	**Other**		
S. pneumoniae	1		*Acinetobacter baumannii*	7		*Haemophilus* spp.	1	0.8
Alpha-hemolytic streptococci	2		*Alcaligenes* spp.	1				
			Pseudomonas spp.	13				
Coryneform bacteria	3		*Stenotrophomonas maltophilia*	6				

CNS: Coagulase-negative staphylococci.

Table 2. Microorganisms from blood culture; results of different centers in Turkey (from 5th Symposium of Febrile Neutropenia -2003 Antalya)

Ref.no	**Center**	**Service**	**Duration/ time**	**No of blood culture isolates**	**Gram-negatives (%)**	**Gram-positives (%)**
6	Erciyes University	HO	2000	245		72.7
		HO	2001	480		75.5
		HO	2002	434		76.6
7	Gazi University	HO	2001-2002	~50	22	72
8	Cerrahpaşa University	H	2000-2002	83	50	49
9	Kartal Lütfi Kırdar Hospital	*	2001-2002	44	57**	43
10	Hacettepe University	HO	1997-2000	113	54	46

HO: Hematology-Oncology, H: Hematology.
* Department undefined.
** Includes results of 44 blood, 21 urine and 7 unexplained cultures.

own endogenous flora[13]. In 1970s gram-negative organisms accounted for 70% of documented bloodstream pathogens in febrile neutropenia, and mortality due to gram-negative sepsis was reported to be as high as 40%[14]. By the mid 1980s gram-positive organisms started to predominate. This was explained by the introduction of prophylactic antimicrobial agents against gram-negative pathogens, mucositis due to intensive chemotherapy, increased use of long term intravascular catheters[15-17]. With an increasing incidence of gram-positive infections especially by CNS new protocols have been introduced[18]. In Turkey in two multicentric studies in 1995-1996 gram-positives predominated in blood culture isolates (69%), in

1997-1998 both gram-positive and negative bacteria were found to be equal[19,20]. During the same period several reports from Turkey showed different results. Some pointed out the importance of gram-negatives as the other s found gram positives to be predominant[21,22]. In our hospital in 1997, gram-negative bacilli were more common (29/54) compared to gram-positives (24/54). There was only one isolate of *Acinetobacter baumannii*[23]. Gram-negative bacteria seem to increase in our hospital. Similar trends towards gram-negatives were also observed in studies from different parts o f the world[24,25]. Gram-negative bacilli were also the predominant isolates in Hacettepe University at the first half of 1990s with significant increase in gram-positive bacteria from 7.5% in 1986-1988 to 28% in 1991-1994[26]. The 3 of 5 studies from febrile neutropenia symposium presented in this paper shows the predominance of gram-negatives. In one report from Erciyes University, the high number of bacteria included in the study makes us think whether skin commensals were not excluded from the study. Also data from Gazi University showed the predominance of gram-positives. In a recent paper published by Kartal Lutfi Kirdar Hospital it is reported that though gram-negatives predominated as the causative agent of febrile neutropenic episodes, gram-positive bacteria (28/49) were prevalent among blood isolates compared to gram- negative isolates (21/49)[27]. There are different reports from different centers in Turkey. This may be due to differences of the patients included in the studies, different chemotherapy protocols and also due to different microbiological and clinical evaluations. Among gram-negatives *E. coli* was the main isolate all over the world and among gram-positives CNS predominated. Our data showed similar results. One important point about our study is the high incidence of nonfermentatives. Previous studies from our hospital revealed *A. baumannii* to be rare. In our study *A. baumannii* (7 isolates) and *Stenotrophomonas maltophilia* (6 isolates) were remarkable[23]. Among gram-positives CNS was the most common species. *Stenotrophomonas* has been considered to have limited pathogenity but report on serious infections has been a serious concern mostly in immunocompromised persons with significant mortality attributable to this microorganism. The factors found to be most commonly associated with *S. maltophilia* bacteremia were presence of malignancy, increased duration of hospitalization before bacteremia, previous receipt of broad–spectrum antibiotic therapy, presence of central vascular catheters and prolonged neutropenia[28-30]. The distribution of isolation rate of the nonfermentative bacteria including *S. maltophilia*, to different months helps us to eliminate nosocomial epidemics.

Gram-negative bacteria *E. coli* and *Klebsiella* spp. are the main microorganisms isolated from blood cultures of febrile neutropenic patients in our hospital. The increasing incidence of nonfermentative gram-negative bacteria (*A. baumannii* and *S. maltophilia*) was remarkable.

REFERENCES

1. Rolston KVI, Raad R, Whimbey, et al. The changing spectrum of bacterial infections in febrile neutropenic patients. In: Klastersky JA (ed). Febrile Neutropenia. New York: Springer, 1997:53-6.
2. Bodey GP, Buckley M, Sathe YS, Friereich EJ. Quantitative relationship between circulating leucocytes and infections in patients with acute leukemia. Ann Intern Med 1966;64:328-40.
3. Febril Nötropenik Hastalarda Tanı ve Tedavi Kılavuzu (FEN Çalışma Grubu) Ankara: Bilimsel Tıp Yayınevi, Şubat 2003.
4. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections. Am J Infect Cont 1988;16:128-40.
5. Konemann EW, Allen SD, Janda WM, Schreckenberger PC, Winn WC. Color Atlas and Textbook of Diagnostic Microbiology. 4th ed. Philadelphia: JB Lippincott Company, 1992.
6. Eser B, Yıldız O, Abravcı NÖ, et al. Hematolojik maligniteli hastalardan izole edilen bakteriler ve antibiyotik duyarlılıkları: Erciyes Üniversitesi Dedeman Hastanesi üç yıllık takip sonuçları. 5. Febril Nötropeni Simpozyumu Özet Kitabı. Şubat 2003:147.
7. Güzel Ö, Şenol E, Yağcı M, Haznedar R. Maligniteli hastalardan izole edilen mikroorganizmaların spekt-

rumları ve direnç paternleri. 5. Febril Nötropeni Simpozyumu Özet Kitabı. Şubat 2003:149.

8. Özaras R, Öngören Ş, Ar C ve ark. Febril nötropenik hastalarda etkenler ve duyarlılıkları. Febril Nötropeni Simpozyumu Özet Kitabı. Şubat 2003:152.
9. Gencer S, Batırel A, Özer S. Febril nötropenik hastalarda infeksiyon etkenlerindeki değişiklikler. 5. Febril Nötropeni Simpozyumu Özet Kitabı. Şubat 2003: 153.
10. Zarakolu P, Güven GS, Şardan YÇ, et al. Hematolojik kanserli hastaların kan kültürlerinden izole edilen bakteriler ve antimikrobiyal duyarlılıkları. 5. Febril Nötropeni Simpozyumu Özet Kitabı. Şubat 2003:154.
11. Schimpff S, Satterlee W, Young V, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. New Engl J Med 1971;284:1061-5.
12. Bill J. Laboratory diagnosis of infections in febrile neutropenic or immunocompromised patients. Int J Antimicrob Agents 2000;16:87-9.
13. Schimpff SC, Young VM, Greene WH, et al. Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. Ann Intern Med 1972;77:707.
14. Klastersky J. Concept empiric therapy with antibiotic combinations: Indications and limits. Am J Med 1986;80:2-12.
15. Winston DJ, Dudnick DV, Chapin M, Ho WG, Gale RP, Martin WJ. Coagulase-negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 1983;143:32-6.
16. Durand-Gasselin B, Leclerq R, Girard-Pipau F, et al. Evolution of bacterial susceptibility to antibiotics during a six year period in a haematology unit. J Hosp Infect 1995;29:19-33.
17. Gram positive bacteraemia in granulocytopenic cancer patients. EORTC International Antimicrobial Therapy Cooperative Group. Eur J Cancer 1990; 26:569-74.
18. Lim SH, Smith MP, Goldstone AH, Machin SJ. A randomized prospective study of ceftazidime and ciprofloxacin with or without teicoplanin as an empiric antibiotic regimen for febrile neutropenic patients. Br J Haematol 1990;76(Suppl 2):41-4.
19. Akova M, Akan H, Korten V, et al. Comparison of meropenem with amikacin plus ceftazidime in the empirical treatment of febrile neutropenia: A prospective multicentre trial in patients without previous prophylactic antibiotics. Int J Antimicrob Agents 1999;13:15-9.
20. Erman M, Akova M, Akan H, et al. Comparison of cefepime and ceftazidime in combination with amikacin in the empirical treatment of high risk patients with febrile neutropenia: A prospective, randomised, multicenter study. Scand J Infect Dis 2001;33:827-31.
21. Eser B, Çetin M, Ünal A, Altınbaş M, Doğanay M. Kanserli hastalarda bakteriyel ve fungal infeksiyon etkenleri. 3. Febril Nötropeni Sempozyum Program ve Özet Kitabı. Antalya, 1999:81.
22. Büyükberber N, Büyükberber S, Özerol İ, Harputluoğlu M, Ak G, Sarı R. Febril nötropenide infeksiyon yerleri ve etkenleri. 3. Febril Nötropeni Sempozyum Program ve Özet Kitabı. Antalya, 1999:85
23. Aksu G, Ruhi MZ, Bengisun S, Üstün C, Özenci H, Akan H. AÜTF Hematoloji kliniğinde yatan febril nötropenik hastaların mikrobiyolojik olarak saptanan infeksiyon etkenleri. 3. Febril Nötropeni Sempozyum Program ve Özet Kitabı. Antalya, 1999:89.
24. Aquino VM, Pappo A, Buchanan GR, et al. The changing epidemiology of bacteremia in neutropenic children with cancer. Pediatr Infect Dis J 1995; 14:140-3.
25. Collin BA, Leather HL, Wingard JA, Ramphal R. Evolution incidence and susceptibility of bacterial bloodstream isolates from 519 Bone Marrow Transplant patients. Clin Infect Dis 2001;33:947-53.
26. Sain G, Hayran M, Ünal S, et al. Nötropenik ateşli kanser hastalarında infeksiyon. 3. Febril Nötropeni Sempozyum Program ve Özet Kitabı. Antalya, 1999:111.
27. Gencer S, Batırel A, Özer S. Febril nötropenik olgulardan infeksiyon etkeni olarak izole edilen bakteriler ve antibiyotik duyarlılıkları. Flora 2003;8:207-12.
28. Koll BS, Brown AE. The changing epidemiology of infections at cancer hospitals. Clin Infect Dis 1993; 17(Suppl 2):322-8.
29. Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. Clin Microbiol Rev 1998;11:57-80.
30. Senol E, Jardin J, Stark P, et al. Attributable mortality of *Stenotrophomonas maltophilia*. Clin Infect Dis 2002;34:1653-16.

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