Bacterial Spectrum and Antimicrobial Susceptibility Pattern of Bloodstream Infections in Children with Febrile Neutropenia: Experience of Single Center in Southeast of Turkey

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Abstract Empirical antimicrobial therapy is usually started in febrile neutropenic patients without having culture results. The aim of this study was to help determine the policies of empirical antibiotic usage in febrile neutropenic children by detecting the antimicrobial susceptibility profile in this group of patients. In this study 811 blood cultures taken from neutropenic children hospitalized at the Department of Oncology of Gaziantep Children Hospital November 2007 and February 2010 were retrospectively evaluated. Blood cultures were routinely collected in aerobic and anaerobic media and incubated using the BACTEC system. Identification and antimicrobial susceptibility testing of the isolates to antimicrobial agents was performed using the Vitek2[®] system according to the recommendations of the Clinical and Laboratory Standards Institute. Of 811 isolates analyzed, 128 (56.4%) were gram positive cocci, 43 (18.9%) were gram negative bacilli and fungi accounted for 56 (24.7%). The main isolated Gram-positive bacteria from blood were *coagulase-negative staphylococcus* (56.7%), followed by methicillin-resistant *Staphylococcus aureus*

(14.1%). *S. aureus* and *Streptococcus spp.* were all susceptible to linezolid, vancomycin and teicoplanin. *S. aureus* was still susceptible to few other antimicrobial agents such as tetracycline (82.4%), chloramphenicol (55.6%). Seven *E. faecium*, 7 *E. fecalis* and 1 *E. hirae* was isolated from blood cultures. Vancomycin resistance was detected in 6 out of 15 (40%) *Enterococcus spp.* isolates. Among gram-negative bacteria *E. coli* (30.2%) was followed by *Klebsiella pneumoniae* (20.9%) and *Proteus spp.* (18.6%). Imipenem (89.2%), meropenem (86.6%), chloramphenicol (88.9%), amikacin (82.4%) and fosfomycin (81.3%) showed highest susceptibility in vitro activity against all Gram-negative isolates. To know the antimicrobial susceptibility profile of the pathogens frequently isolated from febrile neutropenic children and to consider this profile before starting an empirical antibiotic therapy would help the clinics which have any role in the treatment of these patients to determine the empirical antibiotic usage policies.

Keywords Febrile neutropenia · Antibiotic susceptibility · Children

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Introduction

Infection is still a frequent and serious problem in cancer patients treated with chemotherapy who then becomes neutropenic. Despite major advances in the therapy of febrile neutropenia (FN), including more effective and less toxic empirical broad-spectrum antibiotics that can be used as outpatient therapy in selected low-risk patients, availability of better empirical antifungal regimens in patients who do not respond to standard antibiotics and increased use of standard and long-acting granulocyte colony-stimulating factors, febrile neutropenia still remains a very

difficult therapeutic problem with a significant mortality rate. The most severe bacterial infections in these patients are bloodstream infections (bacteraemia) with or without a site of primary infection. The Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG) trials had a 32% rate of bacteraemia in 1973, which dropped to 22% in 1994 [1]. However, their experience was that the proportion of Gram-positive and Gram-negative pathogens causing bacteraemia changed over this time period. The proportion of Gram-negative and Gram-positive pathogens went from 71 and 29%, respectively, in 1973–1978 to 33 and 67% in 1992–1994 [1]. But since the beginning of the new century, Gram-negative bacilli have re-emerged [2].

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. The study was also conducted to assess the isolation rate of bacterial and fungal causative agents in febrile neutropenic episode.

Materials and Methods

Study Design

In this study 811 blood cultures obtained from neutropenic patients hospitalized at the Departments of Pediatric Oncology of Gaziantep Children Hospital between November 2007 and February 2010 were retrospectively evaluated. Blood cultures were routinely collected in aerobic and anaerobic media and incubated using the BACTEC system (Becton–Dickinson Diagnostic Systems, USA). Identification and antimicrobial susceptibility testing of the isolates to antimicrobial agents was performed using the Vitek2® system (bioMérieux, France) according to the recommendations of the Clinical and Laboratory Standards Institute [CLSI] [3]. Extended spectrum of beta lactamase (ESBL) confirmation was performed using a confirmation test with disks; cefotaxime versus cefotaxime/clavulanate and ceftazidime versus ceftazidime/clavulanate as described in the CLSI guidelines. ESBL was interpreted as present whenever the inhibition zone around the disk containing clavulanate was at least 5 mm larger than that of the disk containing the same cephalosporin but without clavulanate. *E. coli* ATCC 25922 and *K. pneumonia* ATCC 700603 strains were used as controls.

Results

Two hundred and twenty-seven pathogens were evaluated as pathogens. Gram-positive cocci were the most

Table 1 Isolated pathogens from blood cultures

General	Species	n	%
Gram positive cocci		128	56.6
	<i>CNS</i>	72	31.7
	<i>MRSA</i>	18	7.9
	<i>Streptococcus</i> spp.	18	7.9
	<i>Enterococcus</i> spp.	15	6.6
	<i>MSSA</i>	2	0.9
	<i>Group A beta hemolytic streptococcus</i>	1	0.4
	<i>Alpha hemolytic streptococcus</i>	1	0.4
Gram negative bacilli		42	18.6
	<i>E. coli</i>	13	5.7
	<i>K. pneumoniae</i>	9	4.0
	<i>Proteus</i> spp.	8	3.5
	<i>P. aeruginosa</i>	3	1.3
	<i>Neisseria</i> spp.	3	1.3
	<i>S. maltophilia</i>	3	1.3
	<i>M. morganii</i>	2	0.9
	<i>Salmonella</i> spp.	2	0.9
	<i>C. fetus</i>	1	0.4
Fungi	<i>Candida</i> spp.	56	24.7
Total		227	100

CNS Coagulase-Negative *Staphylococci*, *MRSA* Methicillin Resistance *S. aureus*, *MSSA* Methicillin sensitive *S. aureus*

frequently isolated cause of infectious agents, accounting for 128 (56.4%) of the total number. Gram-negative organisms accounted for 43 (18.9%) and fungi accounted for 56 (24.7%) of the total number of isolated agents. Results of isolated agents are summarized in Table 1.

The main isolated Gram-positive bacteria from blood were *Coagulase-Negative Staphylococcus* (*CNS*) (56.7%; 72 *CNS* isolates out of 128 total Gram-positive blood isolates), followed by methicillin-resistant *Staphylococcus aureus* [*MRSA*] (14.1%; 18 *MRSA* isolates out of 128 total Gram-positive blood isolates). Staphylococcal, streptococcal and enterococcal isolates showed various patterns of resistance.

Staphylococcus aureus and *Streptococcus* spp. were all susceptible to linezolid, vancomycin and teicoplanin. *S. aureus* was still susceptible to few other antimicrobial agents such as tetracycline (82.4%), chloramphenicol (55.6%). However, they showed higher resistance rates to most other antimicrobial agents tested including 90% resistance to methicillin (Table 2). *Streptococcus* spp. were still susceptible to few other antimicrobial agents such as chloramphenicol (100%), tetracycline (87.5%), rifampicin (80%).

Seven *E. faecium*, 7 *E. faecalis* and 1 *E. hirae* was isolated from blood cultures. Vancomycin resistance was

Table 2 Percentage of antimicrobial susceptibility of gram-positive isolates

Antimicrobial	CNS	MRSA	MSSA	<i>Streptococcus</i> spp.	<i>Enterococcus</i> spp.
Chloramphenicol	92.3	55.6	50	100	80
Ciprofloxacin	61.5	–	–	–	100
Levofloxacin	62.5	–	50	–	66.7
Moxifloxacin	61.8	–	50	–	77.8
Tetracycline	81.7	82.4	50	87.5	64.3
Trimethoprim/sulfamethoxazole	52.1	38.9	100	40	21.4
Vancomycin	100	100	100	100	60
Teicoplanin	100	100	100	100	66.7
Linezolid	100	100	100	100	100
Eritromycin	22.4	16.7	100	64.7	7.1
Rifampicin	37.1	50	50	80	100
Azithromycin	4	12.5	50	0	0
Penicillin G	0	0	50	20	0

CNS Coagulase-Negative
Staphylococci, MRSA
Meticilline Resistance
S. aureus, MSSA Meticilline
sensitive *S. aureus*

detected in 6 out of 15 (40%) *Enterococcus* spp. isolates. Five of them were *E. faecium* and one of them was *E. fecalis*.

Escherichia coli (*E. coli*) (30.2%; 13 out of 43 total Gram-negative isolates) was the most prevalent agent among all causative bacteria. Among gram-negative bacteria *E. coli* was followed by *Klebsiella pneumoniae* (20.9%) and *Proteus* spp. (18.6%). A number of less-frequent Gram-negative bacteria were isolated and identified (*Pseudomonas aeruginosa*, *Neisseria* spp., *Stenotrophomonas maltophilia*,

Morganella morganii, *Salmonella* spp. and *Campylobacter fetus*).

The anti-microbial activity of various types of antimicrobial agents against *E. coli* isolates from bloodstream of children is shown in Table 3. Among all the antimicrobials used, carbapenems (imipenem, meropenem, ertapenem), chloramphenicol, cephalosporins (cefotaxime, cefepime) cefaperazone/sulbactam, fosfomycin and piperacillin/tazobactam showed highest in vitro activity against *E. coli* strains. Amikacin showed lowest in vitro activity against

Table 3 Percentage of antimicrobial susceptibility of gram-negative isolates

Antimicrobial	All isolates	<i>E. coli</i>	<i>Klebsiella pneumoniae</i>	Other enteric bacteria	<i>P. aeruginosa</i>	<i>S. maltophilia</i>
Amicasin	82.4	7.7 ^a	55.6	62.5	100	–
Gentamicin	72.2	69.2	33.3	81.3	100	–
Ceftazidime	58.8	15.4 ^a	33.3	72.7	0	–
Cefotaxime	70	100	0	62.5	0	–
Cefepime	84.4	100	55.6	100	50	–
Cephazoline	40	80	0	0	–	–
Ceftriaxone	53.6	77.8	33.3	70	0	–
Cefaperazone/sulbactam	93.3	100	66.7	100	–	–
Imipenem	89.2	100	100	100	66.7	0
Meropenem	86.6	100	100	100	50	0
Ertapenem	55.6	100	20	100	–	–
Ciprofloxacin	53.3	66.7	42.9	40	50	–
Levofloxacin	60	66.7	42.9	100 ^a	100	100
Chloramphenicol	88.9	100	0	100	–	–
Tetracycline	73.7	83.3	0	90.9	0	–
Trimethoprim/sulfamethoxazole	71.1	76.9	33.3	100	0	100
Nitrofurantoin	35.7	100	14.3	100	0	–
Fosfomycin	81.3	100	100	60	33.3	–
Piperacillin/tazobactam	81	100	42.9	100	–	–

^a Medium susceptibility

E. coli strains. In case of *K. pneumoniae*, carbapenem group (imipenem, meropenem) and fosfomycin were found to be more effective compared to cephalosporins and aminoglycosides (Table 3). *Stenotrophomonas maltophilia* was detected only in 3 blood culture. Only levofloxacin and trimetoprim/sulfamethoxazole showed in vitro activity against *Stenotrophomonas maltophilia*. There were 12 ESBL producing Gram-negative bacilli (3 *E. coli* and 6 *K. pneumoniae*).

Discussion

During the past several decades, the nature of bacteremia in febrile neutropenic patients as reported in the European and American literature has undergone significant fluctuations. The main change reported has been the reduction in the occurrence of bacteremia due to gram-negative organisms, with a shift to gram-positive organisms [4, 5]. The causes of this change in the epidemiology of the infection have not been clearly identified, but they may include more aggressive radiotherapy and chemotherapy, more profound and prolonged neutropenia, increased use of intravenous catheters, and selective pressure of antibiotics [4, 5].

It was previously reported that identification of the causative microorganisms of infection is possible in only 22–39% of cases [6–8]. In the present study blood culture positivity accounted for 223 of 811 (27.5%) total blood cultures over a two and a half years period. This prevalence is comparable to other series. In a multi-center study, carried out to determine the causative agents of bacteremia in children with cancer, the most frequently isolated pathogens were CNS (43%), *S. aureus* (16%), *E. coli* (9%), *Klebsiella* spp. (8%), *Pseudomonas* spp. (5%) and *Candida* spp. (4%) [9]. In another multi-center surveillance study conducted in 18 pediatric hematology centers over a 1-year period, Gram-positive cocci caused 45% (85/191) of the episodes, Gram-negative rods 41% (78/191) and fungi 9%; whereas 5% of the episodes were polymicrobial infections [10].

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 [11]. 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 [12]. As it is obviously seen, there are significant differences in the epidemiological profiles among the areas in our country. In the present study, Gram-positive cocci were found to account for 56.4% of the total isolates. The most common Gram-positive causative agents of bloodstream infections in this study were CNS (31.7%), *S. aureus* (8.8%) followed by *Streptococcus* spp. (7.9%). This result is similar to other studies. Additionally, an

increasing frequency of infections caused by fungi and an increased mortality due to them has been reported [13]. Fifty-six out of 226 positive cultures were *Candida* spp. in our study.

The incidence of streptococcal infections in cancer patients has also been rising for the past years and the viridans streptococci have now become one of the most frequent organisms from blood-stream infection in neutropenic patients [14]. *S. viridans* accounted for 7.9% of isolated microorganisms from all patients in our study. Group A beta-hemolytic streptococcal infection is an extremely rare causative agent in children with cancer. Only one group A beta-hemolytic streptococcus was isolated in our study.

Although data from clinical trials and surveillance studies of in vitro activity are a basic guide to the choice of an empirical antibiotic regimen, other factors should be taken into account in each institution, including local environmental characteristics that affect the nosocomial microflora and its resistance patterns, as well as antibiotic toxicity, cost of care, and patient-related factors [15]. Resistance patterns of pathogens isolated from febrile neutropenic patients have emerged as a significant challenge.

Resistance to vancomycin among enterococci has emerged as a general problem and is now found among isolates from febrile neutropenic patients, among whom outbreaks of vancomycin-resistant enterococcal infections have been reported in oncology units [16]. In addition, there is concern about the possibility of this resistance being transferred on a larger scale to staphylococci in vitro [17], as has occurred in vivo [18]. Resistance among viridans streptococci, especially *S. mitis* and *S. salivarius*, has also become an issue. In a study by Carratalá et al. [19] in Barcelona, only slightly more than 20% of viridans streptococcal isolates from febrile neutropenic patients remained susceptible nearly 40% to penicillin. More than 95% were susceptible to vancomycin, whereas susceptibility rates to cefotaxime, erythromycin, and imipenem were nearly 50, 57, and 67%, respectively.

Eurosurveillance study revealed that, Mediterranean region had a high prevalence region for MRSA, it was reported MRSA was nearly 40% in Turkey [20].

In our country, Celkan et al. [21] showed 50% of *S. aureus* isolates and 18% CNS isolates had a methicillin resistance in pediatric hematology-oncology department between 2000 and 2004. In our study methicillin-resistant *S. aureus* accounted for 90% of staphylococcal isolates. In a similar study, a significant increase in Gram-positive antibiotic resistance was noted: 55% of CNS were resistant to methicillin, 44% of *S. aureus* were resistant and the resistance of *Streptococcus* spp. to penicillin reached to 50% [9].

Enterococci are important hospital-acquired pathogens. Isolates of *E. faecalis* and *E. faecium* are the third- to fourth-most prevalent nosocomial pathogen worldwide. *Enterococcus* species have also recently emerged as important pathogens in patients with cancer. Colonization with vancomycin-resistant enterococcus (VRE), chemotherapy, neutropenia, mucositis, surgery and severe illness are risk factor for VRE bacteremia [22]. Acquired resistance, most prominently to penicillin/ampicillin, aminoglycosides (high-level resistance) and glycopeptides are reported in an increasing number of isolates and the therapeutic spectrum in these cases is limited. VRE is an important problem in Europe, and its prevalence is increasing by the years [23]. The VRE infections are reported in a high rate in Greece and Ireland however it is in a lower rate in Nordic countries.

During the susceptibility survey performed in 2000 of enterococci isolated European hospitals, no vancomycin resistant *E. faecium* strains were detected in Turkey [24]. After that time, VRE was reported in many hospitals in our country [25–28]. Fifteen *Enterococcus spp.* was identified in our serie. Vancomycin resistance was detected in 6 out of 15 (40%) *Enterococcus spp.* isolates. Five of them were *E. faecium* and one of them was *E. faecalis*. This result showed that *Enterococcus spp.* was an important isolated agent in immunosuppressive patients.

Data taken from two recent publications concerning isolates recovered at cancer centers, give a general picture of the situation in the United States, which may not be applicable to all parts of the world. The highest rates of susceptibility are seen with cefepime and imipenem, which are active against almost 100% of *E. coli*, *K. pneumoniae*, *Enterobacter* species, and *S. aureus* isolates and maintain reasonable activity against *P. aeruginosa* isolates. Imipenem is, however, the most active agent in vitro against gram-negative organisms that produce ESBLs. These agents have already proven useful in clinical practice for treating febrile neutropenic patients [29, 30]. They have a distinct advantage over ceftazidime in their spectrum of coverage against gram-positive organisms.

In European collaborative studies, the incidence of antibiotic resistant bacteria was higher in southern Europe than in northern and central Europe [31, 32]. A national surveillance programme in Norway showed more than 99% susceptibility to aminoglycosides in blood culture isolates of *E. coli* and *Klebsiella spp.* [33]. Butt et al. [34] showed cefepime resistance was 27% in *E. coli* isolates, and they showed increasing resistance to third-generation of cephalosporins. In this study, resistance rates were reported for Gram-negative pathogens, reaching nearly 35% for ceftazidime, 30% for levofloxacin and ciprofloxacin.

For giving effective first-line empirical antibiotic treatment in febrile neutropenia, it is important to know the

resistance pattern of the hospital and region. Continuous 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 pediatric patients found that 51.6% of isolates were ESBL producers [35]. Taking into account ESBL-producing *E. coli* and *K. pneumoniae* were also found in our study, ESBL-producing microorganisms should be kept in mind when a patient with persistent fever and who does not respond to the given therapy.

In 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. As the etiology of febrile neutropenic infections has shifted from Gram-negative to gram positive organisms in many centers, our results also show that infections with gram positive bacteria predominates in febrile neutropenic attacks in our center.

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