BLOODSTREAM INFECTIONS IN FEBRILE NEUTROPENIC PATIENTS: BACTERIAL SPECTRUM AND ANTIMICROBIAL SUSCEPTIBILITY PATTERN

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Background: Bacterial infections are the major cause of morbidity and mortality among neutropenic patients. Prompt administration of empiric antimicrobial therapy for febrile neutropenic patients is considered vital. Before putting neutropenic patients on empiric antimicrobial regimens, it is essential to be aware of the spectrum of locally prevalent pathogens and their susceptibility pattern. **Methods**: We studied the bacterial spectrum and antimicrobial susceptibility pattern of organisms causing bloodstream infections in febrile neutropenic patients in Armed Forces Bone Marrow Transplant Centre, Rawalpindi and the Department of Oncology, Combined Military Hospital, Rawalpindi over a period of nine months from January to September 2002. **Results:** Blood specimens for culture and susceptibility testing were collected from 158 febrile patients with neutropenia. Eighty-three organisms were isolated from 60 patients. Thirty-six (43%) isolates were Gram-positive cocci and forty-seven (57%) were Gram-negative rods. Among the Gram-positive cocci, coagulase negative staphylococci (CoNS) were the predominant pathogens (26%), followed by *Staphylococcus aureus* (8%). Among Gram-negative rods, *Escherichia coli* was the predominant isolate (13%) followed by *Klebsiella pneumoniae* (10%), *Acinetobacter johnsonii* (10%) and *Pseudomonas aeruginosa* (7%). Nine specimens yielded polymicrobial growth. Forty percent of *Staphylococcus aureus* and 55% of CoNS were resistant to methicillin. All the Gram-positive isolates were susceptible to vancomycin and teicoplanin. Among the Gram-negative rods, there was 100% resistance to ampicillin, 65% to gentamicin, 47% to amikacin and 66% to third generation cephalosporins. All the gram-negative isolates were susceptible to imipenem. **Conclusion:** The spectrum of isolates among febrile neutropenic patients in our population appears to be shifting towards Gram-positive microorganisms. Due to increasing levels of drug resistance among the isolates, a glycopeptide in combination with a carbapenem would be a prudent choice as empiric therapy in high-risk cases.

Keywords: Neutropenia; infection; fever; empiric therapy; Pakistan.

INTRODUCTION

Immuno-deficient states are associated with increased risk of infections. Malignancies and cytotoxic chemotherapy used to treat these malignancies are important causes of deficient immunity. The most important manifestation of the immuno-deficient state in such cases is neutropenia.[1,2] Between 48-60% of neutropenic patients who develop fever have an infection.[3] These infections can be life threatening and are responsible for high morbidity and mortality.[1,2,4] Increasing use of cytotoxic chemotherapy for various malignancies has led to an increase in the population of neutropenic patients. Although neutropenia itself is the single most important risk factor for infections, the risk increases with the severity and duration of neutropenia.[5] If the neutropenia lasts for more than five weeks, the frequency of infections is 100%.[2]

Prompt administration of empiric antimicrobial therapy for febrile neutropenic patients is considered vital and has been standard for the last three decades.[5,6] Before putting neutropenic patients on empiric antimicrobial regimens, it is essential to be aware of the spectrum of locally prevalent pathogens and their susceptibility patterns.[4]

Keeping this in mind, we planned our study to determine the spectrum and antimicrobial susceptibility pattern of bacteria causing bloodstream infections in febrile neutropenic patients undergoing cytotoxic chemotherapy and bone marrow transplantation in military hospitals in Rawalpindi, Pakistan.

MATERIAL AND METHODS

The study was carried out at the Department of Microbiology, Armed Forces Institute of Pathology, Rawalpindi in collaboration with Armed Forces Bone Marrow Transplant Centre, Rawalpindi and the Department of Oncology, Combined Military Hospital, Rawalpindi over a period of nine months from January to September 2002.

The bacterial spectrum and antimicrobial susceptibility pattern of organisms causing bloodstream infections was studied in all hospitalized febrile neutropenic patients suffering from various types of malignancies and haematological disorders, and those undergoing anticancer therapy and bone marrow transplantation. No discrimination was made on the basis of age or gender. Patients already on antimicrobial therapy and those having fever due to non-infectious causes, such as blood transfusion, drug infusion etc. were excluded from the study. All the patients were subjected to a thorough physical examination, complete blood counts, routine blood chemistry, urine examination and chest radiography. Fever was defined as a single oral temperature of $\geq 38.3^0$ Centigrade (101^0 F) or a temperature of $\geq 38^0$ C for $\geq$ 1 hour.[3] Neutropenia was defined as an absolute neutrophil count of <500 per cubic millimeter.[5]

Blood specimens for culture and antimicrobial susceptibility testing were obtained from peripheral veins when the patients developed fever. When intravenous catheter-related bloodstream infection (CR-BSI) was suspected, to rule out contamination, blood specimens were obtained from the lumen of the device as well as from a peripheral vein.[2,3] A simultaneous peripheral vein blood specimen was also obtained when catheter tip cultures were performed.[2] The site of specimen collection (peripheral vein, from catheter lumen or tip) was not further analyzed.

Immediately after collection, 5-7 ml blood was directly added to brain heart infusion (BHI) broth or to a Signal Oxoid blood culture bottle (Oxoid, Hampshire, UK), and 8-9 ml thioglycolate broth for anaerobes. If the fever persisted for more than two hours, another sample for blood culture was obtained from a different site and empirical antimicrobial therapy started. The blood culture bottles were incubated at 37^0 C for up to 7 days and regular subcultures were done. A blood culture was considered to be positive if ≥1 bottle grew an organism, with the exception of coagulase-negative staphylococci (CoNS), which required 2 separate positive cultures from blood or one positive blood culture along with the same microorganism from intravascular catheter to be considered as a true cause of bacteremia.[7] Identification of the isolates was done by Gram staining and standard biochemical tests. Antimicrobial susceptibility testing was done by the modified Kirby-Bauer disk diffusion technique and the results were interpreted according to the recommendations of National Committee for Clinical Laboratory Standards (NCCLS).[8]

All the data collected and microorganisms isolated were presented as proportions (percentages). SPSS for Windows version 10.0 (SPSS Inc., Chicago, IL., USA) was used for data compilation and calculation. P-values of <0.05 were taken as significant and Chi-square test was used to determine the significance of differences between categorical variables.

RESULTS

One hundred and fifty eight patients were included in the study. Out of these, 121 were males and 37 were females. Mean age±SD of the patients was 33.6±17.4 years (range 1-70 years). Seventy-five patients were admitted to the oncology ward and 83 to the bone marrow transplant centre. The patients were suffering from solid organ tumours (*n*=15), leukemias (*n*=74), lymphomas and multiple myeloma (*n*=19) and other haematological disorders including thalassemia and aplastic anaemia (*n*=50).

Table-1: Bacterial spectrum of isolates (*n*=83) from blood of febrile neutropenic patients

Bacterial spectrum	Number (%)
GRAM-POSITIVE COCCI	36 (43.37%)
Coagulase negative staphylococci	22 (26.5%)
Staphylococcus aureus	7 (8.43%)
Enterococcus faecalis	4 (4.81%)
Streptococcus group D (non-enterococcus)	2 (2.4%)
Streptococcus pyogenes	1 (1.2%)
GRAM-NEGATIVE RODS	47 (56.63%)
Escherichia coli	11 (13.25%)
Klebsiella pneumoniae	8 (9.63%)
Acinetobacter johnsonii	8 (9.63%)
Pseudomonas aeruginosa	6 (7.22%)
Acinetobacter baumanii	3 (3.61%)
Citrobacter freundii	3 (3.61%)
Serratia liquefaciens	2 (2.4%)
Serratia rubidaea	2 (2.4%)
Enterobacter cloacae	2 (2.4%)
Klebsiella oxytoca	1 (1.2%)
Providencia rettgeri	1 (1.2%)

Eighty-three organisms were isolated from the blood of 60 patients. There were no anaerobic isolates. Nine specimens yielded polymicrobial growth while in eleven cases different organisms were isolated from the same patient at different times. Thirty-six (43%) isolates were Gram-positive cocci and forty-seven (57%) were Gram-negative rods (0.5>p>0.1). Among the Gram-positive cocci, coagulase-negative staphylococci (CoNS) were the predominant pathogens (*n*=22), followed by *Staphylococcus aureus* (*n*=7). Among Gram-negative rods, *Escherichia coli* was the predominant organism (*n*=11), followed by *Klebsiella pneumoniae* (*n*=8), *Acinetobacter johnsonii* (*n*=8) and *Pseudomonas aeruginosa* (*n*=6) (Table 1).

Forty percent of *Staphylococcus aureus* (*n*=3) and 55% of CoNS (*n*=12) were resistant to methicillin while half of the isolated *Enterococcus faecalis* (*n*=2) were resistant to ampicillin and imipenem. All the Gram-positive isolates were susceptible to vancomycin and teicoplanin (Table-2).

Table 2. Antimicrobial resistance pattern among Gram-positive cocci (*n*=36) isolated from blood of febrile neutropenic patients.

Antimicrobials (% Resistant)												
Organism	*Meth	P/Am	Aug	Ery	Dox	Cot	Gm	Ak	Ofl	Ch	Van/TecFus	Ipm
CoNS (*n*=22)	12 (55%)	22 (100%)	16 (73%)	17 (77%)	18 (82%)	14 (64%)	14 (64%)	10 (45%)	10 (45%)	17 (77%)	0 (0%)	0 (0%)
S. aureus (*n*=7)	3 (43%)	7 (100%)	3 (43%)	3 (43%)	3 (43%)	3 (43%)	5 (71%)	3 (43%)	3 (43%)	3 (43%)	0 (0%)	0 (0%)
E. faecalis (*n*=4)	-	2 (50%)	-	2 (50%)	2 (50%)	-	-	-	-	-	0 (0%)	2 (50%)
S. pyogenes (*n*=1)	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	-	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Strept Gp D (*n*=2)	-	1 (50%)	-	2 (100%)	2 (100%)	2 (100%)	-	-	2 (100%)	2 (100%)	0 (0%)	0 (0%)

Meth=Methicillin, P=Penicillin, Am=Ampicillin, Aug=Amoxicillin/clavulanate, Ery=Erythromycin, Cot=Co-trimoxazole, Dox=Doxycycline, Gm=Gentamicin, Ak=Amikacin, Ofl=Ofloxacin, Ch=Cephradine, Van=Vancomycin, Tec=Teicoplanin, Fus=Fusidic acid, Ipm=Imipenem

* Methicillin/cloxacillin resistance tested by oxacillin disk

Table 3. Antimicrobial resistance pattern among Gram-negative bacilli (*n*=47) isolated from blood of febrile neutropenic patients.

Antimicrobials (% Resistant)												
Organism	Am	Cot	Dox	Gm	Ak	Ofl	Ctx	Cfp	Fep	Ipm	Tzp	Ch
E. coli (*n*=11)	11 (100%)	11 (100%)	11 (100%)	11 (100%)	9 (82%)	11 (100%)	8 (73%)	-	3 (27%)	0 (0%)	1(9%)	11 (100%)
K. pneumoniae (*n*=8)	8 (100%)	7 (88%)	8 (100%)	7 (88%)	6 (75%)	6 (75%)	1 (13%)	-	0 (0%)	0 (0%)	0 (0%)	7 (88%)
A. johnsonii (*n*=8)	11 (100%)	2 (25%0	5 (63%)	5 (63%)	5 (63%)	3 (38%)	2 (25%)	-	1 (13%)	0 (0%)	1(13%)	5 (63%)
Ps.aeruginosa (*n*=6)	-	-	-	3 (50%)	2 (33%)	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
A. baumanii (*n*=3)	3 (100%)	1 (33%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)	2 (66%)	-	0 (0%)	0 (0%)	0 (0%0	3 (100%)
S. rubidaea (*n*=2)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	0 (0%)	1 (50%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)	2 (100%)
S. liquifaciens (*n*=2)	2 (100%)	2 (100%0	2 (100%0	2 (100%)	1 (50%)	2 (100%)	1 (50%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
K. oxytoca (*n*=1)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
E. cloacae (*n*=2)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
P. rettgeri (*n*=1)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
C. freundii (*n*=3)	3 (100%)	0 (0%)	3 (100%)	3 (100%)	1 (33%)	1 (50%)	3 (100%)	3 (100%)	0 (0%)	0 (0%0	0 (0%)	3 (100%)

Am=Ampicillin, Cot=Co-trimoxazole, Dox=Doxycycline, Gm=Gentamicin, Ak=Amikacin, Ofl=Ofloxacin, Ctx=Cefotaxime, Cfp=Cefoperazone, Fep=Cefepime, Ipm=Imipenem, Tzp=Pipracillin-tazobactam, Ch=Cephradine

Among the Gram-negative rods, there was 100% resistance to ampicillin, 65% to gentamicin, 47% to amikacin, 66% to third generation cephalosporins, 13% to fourth generation cephalosporins and 4% to tazobactam-piperacillin. All the Gram-negative isolates were susceptible to imipenem (Table 3).

DISCUSSION

Bacterial infections in neutropenic patients are a major cause of morbidity and mortality.[1,2,4] Knowledge of the locally prevalent pathogens and their susceptibility patterns is important before putting these patients on empiric antimicrobial therapy. Thirty years ago most of the infections in these patients were caused by aerobic Gram-negative bacilli. Over the last twenty years however, a shift in the bacterial spectrum towards Gram-positive cocci has been reported in the West.[1-3,5] Although the exact cause of this shift is not known, long-dwelling intravascular devices, fluoroquinolone prophylaxis and chemotherapy-induced mucositis have been implicated.[2,9] This trend however has not been prominent in the developing world.[1]

CoNS are the commonest organisms isolated in the Western countries followed by *Staphylococcus aureus*. Other Gram-positive cocci like enterococci and viridans streptococci are increasingly being reported as important causes of infection. Among the Gram-negative bacteria, *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella* sp. are the common pathogens.[1,3,5,10-12] In our study although Gram-negative bacilli (57%) were the predominant isolates, statistically their isolation rate did not significantly differ from Gram-positive isolates ($0.5>p>0.1$). Almost half (43%) of the patients were infected with Gram-positive cocci, CoNS being the commonest (26%). In 1998, Karamat *et al* had reported a predominance of Gram-negative isolates from neutropenic patients in the same setting. Among Gram-positive organisms, *Staphylococcus aureus* was the commonest isolate in their study.[13] A definite shift towards Gram-positive microorganisms has been observed in our study with CoNS as the predominant isolates. This shift has also been noted by Siddiqui and Hossain[14], and Burney *et al.*[15] Reasons for this shift in our population are probably the same as cited above.

A change in the antimicrobial susceptibility pattern of the isolates has also occurred over the past few years. An increase in resistance to most of the commonly used antimicrobials has been noted in our study compared to the data of 1998.[13,15] Resistance to third generation cephalosporins among *Escherichia coli*, the commonest Gram-negative isolate was 73%, to ofloxacin 100% and to cefepime 27%. Almost half of the staphylococci were methicillin-resistant and 50% of enterococci were resistant to ampicillin, erythromycin, doxycycline and imipenem. Increased resistance to aminoglycosides was also noted among the Gram-positive isolates.

Various empiric regimens have been recommended for febrile neutropenic patients. However, it is difficult to adopt a single recommended regimen as not only the spectrum of bacterial isolates varies from one setting to another, but also the results of various studies are not comparable because of differing criteria.[3] Traditionally, a combination therapy of an aminoglycoside with an anti-pseudomonal β-lactam was given. Introduction of cephalosporins and quinolones led to their combination with aminoglycosides or their use as monotherapies.[2-5,10] Carbapenems and piperacillin-tazobactam are also being increasingly used.[2,3] Some studies have continued to emphasize a role for high dose quinolones like ciprofloxacin as a monotherapy in neutropenic patients,[4] while others have recommended newer quinolones like clinafloxacin.[16]

The current empiric regimen for high-risk febrile neutropenic patients being followed in Armed Forces Bone Marrow Transplant Centre Rawalpindi and the oncology unit of Combined Military Hospital Rawalpindi is a combination of piperacillin-tazobactam and amikacin as an initial therapy. Although resistance to piperacillin-tazobactam in our isolates was low, the high percentage of both Gram-positive and Gram-negative isolates resistant to amikacin warrants a review of the empiric regimen. Del Favero *et al*[17] have not reported any significant advantage of adding amikacin to piperacillin-tazobactam. The role of aminoglycosides in empiric treatment of neutropenic

patients in our setting needs to be re-evaluated. In our study, there was no resistance to imipenem among the Gram-negative organisms. Carbapenems can be considered as an alternative to piperacillin-tazobactam especially due to their excellent cover against viridans streptococci and pneumococci[3], and *Serratia rubidaea* which was 100% resistant to piperacillin-tazobactam in our study population.

Isolation of a large number of methicillin-resistant staphylococci from our patients poses a dilemma. While CoNS septicaemia does not pose an immediate risk to the life of the neutropenic patient, delay in treating fulminant infection with methicillin-resistant *Staphylococcus aureus* (MRSA) can result in death in less than 24 hours.[3] Addition of a glycopeptide like vancomycin in the empiric therapy has generated a lot of debate mostly because of the risk of development of resistance especially among enterococci. Various studies in the West have not shown any significant advantage of adding these to the regimen. However, it is generally recommended that a glycopeptide should be added in settings where MRSA or viridans streptococci are a problem[2,3,5] or in high-risk patients. Hughes *et al*[3] have suggested a scoring system for identification of high and low-risk febrile neutropenic patients. Keeping in mind that there was almost 50% methicillin-resistance in our isolates of staphylococci, we feel that it would be prudent to add a glycopeptide to the treatment regimen especially among high-risk cases. If no Gram-positive cocci are isolated after appropriate culturing at 48-72 hours, vancomycin should be discontinued. Vancomycin would also cover enterococci and non-enterococcus streptococci isolated in our study, 50% or more of which were resistant to ampicillin, erythromycin, doxycycline and imipenem.

Newer quinolones especially moxifloxacin have been developed for use against Gram-positive cocci and have shown good activity against MRSA in animal models both *in-vivo* and *in-vitro* with a very low propensity to select for resistance.[18] We have observed excellent *in-vitro* activity of moxifloxacin against MRSA in our laboratory (unpublished data). Moxifloxacin is a potential alternative to glycopeptides. However, its utility in clinical settings remains to be validated and until then we would have to continue to rely on glycopeptides.

In low-risk febrile patients with neutropenia, monotherapy with a carbapenem, cefepime, piperacillin-tazobactam[3] or combination therapy with ciprofloxacin and amoxicillin-clavulanate in adults[3, 19] and cefixime in children can be given.

CONCLUSION

The spectrum of isolates from febrile neutropenic patients in our population appears to be changing with a shift towards Gram-positive microorganisms. At the same time resistance to most of the commonly used antimicrobials is increasing. Continuous surveillance of the spectrum of locally prevalent pathogens and their susceptibility patterns is essential for formulation of empiric therapeutic regimens for these patients.

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