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The Spectrum of Bacterial Infections in Febrile Neutropenic Patients: Effect on Empiric Antibiotic Therapy

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Abstract

The aim of this retrospective analysis was to look at the spectrum of bacterial isolates and their resistance patterns to the commonly used antibiotics in the setting of febrile neutropenia. A total of 127 bacteria were isolated from patients with acute leukemias, lymphoproliferative disorders, aplastic anaemia and various solid tumours. Fifty-four percent organisms were gram negative; while the rest were gram positive. *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus* and *Streptococci* were the commonly isolated organisms. Forty-eight percent organisms were isolated from blood, 16% from urine, 13% from wounds and superficial abscesses and 11% from respiratory tract. *E. coli* exhibited a great degree of resistance to the commonly used antibiotics, such as piperacillin (70%), ofloxacin (50%) and aztreonam (50%). *Pseudomonas* and *Klebsiella* also showed varying degree of resistance against the antibiotics. *Staphylococcus aureus* and *Staphylococcus epidermidis* were almost universally resistant to penicillin and showed a variable degree of resistance to other antibiotics too. Compared to the previous reports, the pattern of bacterial isolates and their resistance to antibiotics has changed over the past years. Aminoglycosides and third generation cephalosporins seem to be the choice of antibiotics for the upfront management of febrile neutropenic patients (JPMA 48:364,1998).

Introduction

Chemotherapy results in neutropenia in a great majority of patients. The patients with hematological and lymphoid malignancies are particularly susceptible¹. Of the total number of patients who develop neutropenia, about 80% have fever². A febrile neutropenic patient requires empiric antibiotic therapy, which should be instituted as early as possible³. Delay in initiation of treatment may result in septicemic shock and is often associated with mortality⁴. The vast majority of neutropenic febrile patients (75-80%) do not have a clinical focus of infection at the time of presentation⁵. Hence, empiric antibiotic therapy is formulated on the knowledge of common bacterial isolates and their sensitivity patterns. Gram negative infections were thought to be the most common offending agents and usually a combination of aminoglycosides and beta lactam antibiotics result in defervescence^{1,2}. However, in the past few years, with increasing usage of indwelling catheters and effective treatment of gram negative infections, there has been a shift in the spectrum of bacterial isolates^{5,6}. Gram positive organisms are now isolated with increasing frequency and gram negative organisms display more resistance to B-lactam and other antibiotics. We report the patterns of isolates as well as their resistance to antibiotics from a single institution in Pakistan.

Patients and Methods

The data was collected retrospectively from all the febrile patients seen under the oncology service with culture proven bacterial isolates over a period of 15 months. Of the 379 bacterial pathogens isolated in this period, 127 were identified when the absolute neutrophil count (ANC) of patients was

less than 500/W. The patients either had hematological or non- hematological underlying malignancies oraplastic anemia, Cultures were obtained from blood, urine, sputum, wound/abscess or any other identifiable focus of infection. Culture and sensitivity were carried out according to the routine procedure in the clinical laboratories of our hospital. Briefly, 5 ml of blood was drawn into each of brain-heart infusion bmth and thioglycollate broth and incubated at 37°C for 24 hours. Gram negative bacteria were identified using API 20E strips and gram positive bacteria by the catalose test, coagulase test, sensitivity to optochin and bacitracin discs. Antibiotic sensitivity was performed on diagnostic sensitivity agar plates by Kirby-Bauer method⁷.

Results

Over a period of 15 months, 127 bacterial isolates were cultured from a total of 85 patients while they were neutropenic and febrile. The majority of patients had acute myeloid leukemia (23/85) or various lymphopmliferative disorders (25/85) including acute lymphoblastic leukemia. Seventeen had aplastic anaemia and 18/85 bad solid tumors. One patient each had multiple myeloma and agranulocytosis. Gram negative bacteria accounted for 69/127 (54.5%) of the isolates. *E. coli* was the single most common organism isolated, followed by *pseudomonas aeruginosa* and *Klebsiella*. Details are shown in Table 1.

Table I. Source of isolation of gram negative organisms.

	Blood	Urine	Stool	Wound	Sputum	Others	Total
<i>E. coli</i>	10	8	0	1	0	1	20
<i>Pseudomonas aeruginosa</i>	7	1	0	2	3	1	14
<i>Klebsiella pneumonia</i>	5	0	0	0	0	0	5
<i>Klebsiella aerogenus</i>	0	4	0	0	0	0	4
<i>Aeromonas hydrophila</i>	1	0	0	0	1	1	3
<i>Enterobacter species</i>	1	1	0	2	0	0	4
<i>Acinetobacter Lwoffii</i>	1	0	0	1	0	0	2
<i>Cirtobacter</i>	2	0	0	0	0	0	2
<i>Acinetobacter</i>	3	0	0	0	0	0	3
<i>Actinobacillus</i>	0	1	0	0	1	2	4
<i>Salmonella paratyphi</i>	0	0	2	0	0	0	2
<i>Shigella Flexerni</i>	0	0	1	0	0	0	1
<i>Bacteroides</i>	1	0	0	0	0	0	1
<i>Flavobacterium</i>	0	0	0	0	0	1	1
<i>Branhamella</i>	0	0	0	0	1	0	1
<i>Hemophilus</i>	0	0	0	0	1	0	1
<i>Vibrio cholera</i>	0	0	1	0	0	0	1
Total	31	15,	4	6	7	6	69

The resistance patterns of the commonly isolated organisms were studied against frequently prescribed antibiotics. The antibiotics included aminoglycosides, B-lactam antibiotics, monolactams, third generation cephalosponns and the quinolones.

Table II. Sources of isolation of gram positive organisms.

	Blood	Urine	Sputum	Wound/Abscess	Others	Total
Staphylococcus aureus	8	1	0	4	2	15
Staphylococcus Epidermidis	5	0	0	1	3	9
Staphylococcus Saprophyticus	1	0	0	1	0	2
Staphylococcus not Aureus	3	1	0	0	0	4
Staphylococcus intermedius	1	0	0	0	0	1
Streptococcal species	3	0	0	3	6	12
Bacillus species	4	0	0	0	0	4
Enterococcus	4	3	1	1	1	10
Streptococcus viridans	1	0	0	0	0	1
Total	30	5	1	10	12	58

Table II shows the resistance patterns of E. coli, pseudomonas and Kiebsiella against various antibiotics. E. coli were resistant to pincillin in 70% cases and 50% were resistant to ofloxacin, amonam and cefixime. Twenty-three percent of the pseudomonas species were resistant to piperacillin, whereas 15% were resistant to aztreonam and ofloxacin.

Gram positive organisms comprised 46% (58/127) of the total bacterial isolates. Staphylococcus aureus was the commonest gram positive organism isolated (15/58), followed by streptococcal species (Table III).

Table III. Antibiotic resistance of gram negative organisms.

Antibiotic	E. coli %	Pseudomonas %	Klebsiella %
Amikacin	5	0	0
Aztreonam	50	15	40
Ceftazidime	0	7	0
Gentamycin	10	15	33
Ofloxacin	50	15	0
Piperacillin	70	23	60
Ceftotaxime	15	0	25

Staphylococcus epidermidis were isolated on 9 occasions. All but one patient with bacteremia secondary to staphylococcus epidermidis had an indwelling venous access catheter at the time of the febrile episode.

Table IV. Antibiotic resistance of gram positive organisms.

Antibiotics	Staph aureus	Staph epidermidis
	%	%
Amikacin	13	11
Clindamycin	13	22
Gentamycin	7	33
Erythromycin	13	0
Cephalothin	7	0
Penicillin	86	100
Cloxacillin	0	11
Vancomycin	0	0

Table IV shows the resistance patterns of staphylococcus aureus and epidermidis. Virtually all the organisms were resistant to penicillin.

Discussion

Gram negative aerobic bacteria have been the predominant- isolated organism from febrile neutropenic patients^{1,3}. Over the past few years there has been a shift of microbial flora from gram negative to gram positive organisms at many cancer centers^{5,6}. This could be attributed to better control of gram negative infections and more frequent use of indwelling venous access devices⁶. An earlier study at our institution revealed gram negative organisms to account for 70% of all infections⁸. The vast majority were pseudomonas which comprised 31% of all the isolates. As a result, a combination of amikacin and piperacillin was used commonly to treat prolonged (more than seven days) neutropenic febrile episodes, whereas ofloxacin was frequently used to treat neutropenia expected to last less than seven days⁹.

The current study demonstrates that gram positive organisms have increased in frequency at this institution. Coagulase negative staphylococcus was isolated with increasing frequency, particularly from patients who had indwelling venous access devices. Gram positive rods of Bacillus species were likewise isolated from four patients. The majority of whom had indwelling catheters. The vast majority of patients in this series (78%) had either lymphoproliferative or myeloproliferative disorders or had aplastic anaemia and as such had prolonged neutropenia. Fungi (candida and aspergillus) were cultured on 18 occasions from the same patient group during the study period. However, they were excluded from the overall analysis, since the aim of this study was to investigate the bacterial infections in neutropenic patients which are important in the early empiric antibiotic management.

The demonstration of nearly 50% of the bacterial isolates to be gram positive organisms is in agreement with several recent reports. Petrilli et al¹⁰ have shown gram positive cocci to account for

52.6% of the infections. Similarly Coullioud et al⁶ showed 56% of 1147 pathogens to be gram positive bacteria. However, majority of their patients had indwelling venous lines at the time of febrile episodes. In our study, 19/28 organisms isolated from patients with indwelling various catheters were gram positive.

A previous study at this institution showed pseudomonas to be isolated on 31% occasions⁸, the current study shows pseudomonas to account for only 11% of the isolates. E. coli were the most frequently isolated organisms(16%). An important features of this study is the demonstration of increasing resistance of E. coli to various antibiotics. Of the 20 isolates, 10 were resistant to quinolones, one of the frequently used drugs for the treatment of such infections¹¹, particularly for those who have low risk neutropenia¹². Piperacillin had been used routinely as an integral part of the neutropenic regimen in the past. Seventy percent of the E. coli were resistant to this antibiotic as well, while 50% E. coli were also resistant to aztreonam, a monolactam frequently used as an alternative to the 'first line' amikacin and piperacillin. E. coli showed 5% and 15% resistance to Aminoglycosides and third generation cephalosponns respectively. Besides E. coli, resistance to quinolones, beta lactam, monolactams and third generation cephalosporin has also emerged forpseudomonas and klebsiella.

Another feature of this study is the fact that isolates obtained from any culture-directed site were included for overall analysis. Many of the studies have used only bacteremic episodes to look at the pattern of isolated organisms^{6,7}. If bacteremic episodes alone were to be considered, 30/61 i.e., nearly half the bacteria were gram positive in this study. This is again consistent with the studies mentioned above. Although the majority of organisms were isolated from blood (48%), followed by urine (16%), wound/abscesses (13%) or sputum and tracheal aspirate (11%), occasionally micro-organism were also isolated from sites such as the ascitic fluid, pleural fluid, CSF etc. Hence, it is imperative that every effort should be made to obtain cultures from all possible sites, particularly as the bacterial spectrum has changed and new resistance patterns have emerged. Demonstration of antibiotic resistance resulted in frequent modifications of treatment in these patients.

It is concluded that the gram positive bacteria have increased as a cause of infection in neutropenic febrile patients, particularly in those with indwelling venous access devices. Multi-drug resistant strains of gram negative organisms have emerged rapidly. This may pose a great problem in early management of these patients. A combination of aminoglycosides and third generation cephalosporin seems to be appropriate for the upfront management at this time. Studies of this nature should be frequently repeated to document the changing pattern of bacterial isolates and the antibiotic resistance which has marked implications in the choice of early empiric antibiotic therapy.

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