BACTERIAL SPECTRUM AND SUSCEPTIBILITY PATTERNS OF PATHOGENS IN ADULT FEBRILE NEUTROPENIC PATIENTS: A COMPARISON BETWEEN TWO TIME PERIODS

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Background: The aim of this study was to study trends in bacterial spectrum and susceptibility patterns of pathogens in adult febrile neutropenic patients during two time periods. **Methods:** We retrospectively reviewed the medical records of 379 adult oncology patients admitted with chemotherapy induced febrile neutropenia at our institute during years 2003 and 2006. **Results:** A total of 151 organisms were isolated during the two calendar years. Gram negative bacteria accounted for 57.6% of organisms, while gram positive organisms accounted for 42.3% of the total isolates. The most common organisms were: *Escherichia coli* (23.1%), *Staphylococcus epidermidis* (13.9%), *Pseudomonas aeruginosa* (12.5%) and *Staphylococcus aureus* (7.9%). The number of gram positive isolates showed an increase from 35% in 2003 to 47.2% in 2006 (p=0.13). During each calendar year, *Staphylococcus epidermidis* and *Staphylococcus aureus* were 100% susceptible to vancomycin and 33% strains of *Staphylococcus aureus* were methicillin resistant. *Escherichia coli* and *Pseudomonas aeruginosa* strains were highly sensitive to piperacillin/tazobactam and amikacin during both time periods. Resistance of *Pseudomonas aeruginosa* strains to ciprofloxacin increased from 0% in 2003 to 50% in 2006 (p=0.03). **Conclusions:** Gram negative organisms are the predominant organisms in adult febrile neutropenic patients at our institute. Initial empirical therapy with piperacillin/tazobactam seems appropriate to cover most gram negative pathogens while vancomycin to be added for suspected gram positive infections. During the two calendar years resistance of *Pseudomonas aeruginosa* strains to ciprofloxacin has significantly increased.

Keywords: Bacterial spectrum, Febrile neutropenic patients, Empirical therapy

INTRODUCTION

Febrile neutropenia is a common complication of cancer treatment. With the evolvement of therapeutic advances, more aggressive approach to treatment of malignancies has been adopted which in turn has resulted in improvement in overall survival. At the same time oncology patients frequently succumb to febrile neutropenia. Studies have reported that 48% to 60% of patients admitted with febrile neutropenia have an infection.[1] These infections can be life threatening and increase both the morbidity and mortality.[2–5]

Over the past decade there has been a considerable change in the spectrum and antibiotic susceptibility patterns of pathogens causing infection in febrile neutropenic patients. Knowledge of locally prevalent pathogens and their sensitivities is essential as it helps guide antimicrobial therapy in neutropenic patients.[6] The most effective empiric antimicrobial regimen must be rapidly administered to febrile neutropenic patients as delay in initiation of treatment may result in septicaemic shock and thus increase mortality.

To have an insight into the spectrum and the trend in antimicrobial susceptibility pattern of febrile neutropenic patients during the two calendar years, we planned this study.

MATERIAL AND METHODS

All clinical and microbiological data was collected retrospectively from adult febrile neutropenic patients admitted at our institute during 2003 and 2006. The patient population consisted of adults (18 years or above) with acute and chronic leukaemia, lymphoma and solid tumours. Patients were included if they had fever greater than 38.5 degrees centigrade on one occasion and with an absolute neutrophil count of less than 0.5×10^9/L.

Cultures were taken from blood in all cases and from urine, stool, tracheal aspirate, sputum or wound depending upon identifiable focus of infection. Blood cultures were processed using the Bactec 9240 blood culture system (Becton Dickinson, Maryland, USA). Organisms were identified according to routine bacteriological procedures. Antibiotic susceptibility testing was performed by disc diffusion method of Bauer and Kirby. Results of these were interpreted according to the Clinical Laboratory Standards Institutes guidelines. When blood cultures drawn within 48 hours displayed isolation of more than one organism, the episode was defined as polymicrobial. SPSS Version 10 was used for data compilation and calculation. Pearson chi square test was used to calculate the p-value. P-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 379 patients with chemotherapy induced febrile neutropenia were admitted at our institute during the two time periods. Table-1 shows the characteristics of patients admitted with febrile neutropenia during the two calendar years. The mean age of study population was 41 years (range 18–81 years). Haematological malignancies were 50.1% (190/379). Bacterial cultures were positive in 119 patients (31%) with 151 isolates during the two calendar years. Polymicrobial growths were 18 and 14 during year 2003 and 2006 respectively.

The most common organisms were: *Escherichia coli* 23.1% (35/151), *Staphylococcus epidermidis* 13.9% (21/151), *Pseudomonas aeruginosa* 12.5% (19/151), *Staphylococcus aureus* 7.9% (12/151), *Acinobacter species* 6.6% (10/151) and *Staphylococcus hominis* 5.9% (9/151) during the two calendar years. Spectrum of gram positive and negative organisms is shown in Table-2. No major differences in microbial spectrum were recorded between the two calendar years. Nine (9.8%) isolates of *Staphylococcus hominis* were isolated in year 2006 (p=0.02).

Table-3 shows the resistance patterns of frequently used antibiotics against commonly isolated pathogens during the two calendar years 2003 and 2006. Both *Staphylococcus epidermidis* and *Staphylococcus aureus* strains were completely susceptible to vancomycin. Resistance of *Staphylococcus aureus* strains to methicillin remained unchanged during the two time periods (p=0.10). *Escherichia coli, Pseudomonas aeuroginosa* and *Klebsiella pneumonia* isolates were highly susceptible to imipenem, amikacin and piperacillin/tazobactum. Resistance of *Pseudomonas aeuroginosa* isolates to ciprofloxacin increased significantly during the two study periods (p=0.03). *Acinetobacter* species isolates were highly susceptibility to cefoperazone/sulbactam alone.

DISCUSSION

Over the past twenty five years there has been a shift in the microbiological spectrum from gram negative to gram positive organisms at many cancer centers.[1,2,4,7] The possible reasons for this shift are better control of gram negative infections with newer ultra broad spectrum antibiotics, fluoroquinolone prophylaxis and increase use of long dwelling intravenous devices.[8,9] This study demonstrates that gram negative organisms are still the predominant pathogens causing bacteraemia in febrile neutropenic patients.

The spectrum of bacterial isolates in our study is similar to what has been reported in both local and international studies. *Coagulase negative staphylococci* were the most commonly isolated gram positive organisms.[1,7,10,11] *Escherichia coli* was the most frequently isolated gram negative pathogen.[1,6,7,12]

Apart from significantly increase resistance of *Pseudomonas aeruginosa* to ciprofloxacin, there have been no major differences in the resistance pattern of microorganisms to commonly used antibiotics during the two calendar years. In our study both *Staphylococcus epidermidis* and *Staphylococcus aureus* showed 100% sensitivity to vancomycin which is in agreement with studies by Burney and Blahova *et al*.[2,7] The prevalence rate of methicillin resistant *Staphylococcus aureus* differs markedly among different centres in Pakistan, with 40% in the study by Butt el al and 8% in the study by Khan *et al* and upto.[1,3] Our findings are consistent with the former study with 33% strains of *Staphylococcus aureus* resistant to methicillin during both time periods.

Resistance of *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia* strains to fluroquinolones are on the rise at many cancer centers.[2,3,5] Similarly at our institute, resistance of *Pseudomonas aeruginosa* strains to ciprofloxacin has increased significantly during the two study periods. Extensive use of ciprofloxacin as a prophylactic antibiotic in cancer patients receiving chemotherapy is likely associated with this change. Therefore it is suggested that ciprofloxacin should no longer be the antibiotic of choice for prophylaxis of bacterial infections in our setting.

In recent years, an increasing proportion of infections in neutropenic cancer patients are caused by organisms which have multi-drug resistance. In our setting *Acinetobacter* is one of them.[13] Cefoperazone/ sulbactim should be the antibiotic of choice for treating infections caused by this organism.

We use piperacillin/tazobactam for the empirical treatment of febrile neutropenic patients as studies have shown that piperallacin/tazobactim monotherapy is safe and effective.[14,15] Imipenem is used as an alternative to piperacillin/tazobactam. Vancomycin is only added to empirical treatment if patients present with septicaemia or have soft tissue infection or have prior colonisation with methicillin resistant *Staphylococcus aureus*.

Table-1: Characteristics of patients admitted with febrile neutropenia during calendar years 2003 and 2006

Total patients	**Year 2003**	**Year 2006**
n = 379	n = 113	n = 266
Mean age	40 years	42 years
Sex		
Males	61 (54%)	149 (56%)
Females	52 (46%)	117 (44%)
Haematological Malignancies	41 (36.3%)	149 (56%)
Solid Malignancies	72 (63.7%)	116 (43.6%)
Bacterial cultures positive	42 (37.1%)	77 (28.9%)
Polymicrobial growths	18 (15.9%)	14 (5.2%)

Table-2: Spectrum of gram positive and negative organisms isolated during Years 2003 and 2006

Organisms	Year 2003	Year 2006	*p*-value
Gram positive organisms	**21 (35%)**	**43 (47.2%)**	0.13
Staphylococcus epidermidis	10 (16.6%)	11 (12.0%)	0.18
Streptococcus group A	2 (3.3%)	0	--
Streptococcus group D	2 (3.3%)	3 (3.2%)	0.72
Streptococcus untypable	0	5 (5.4%)	0.10
Staphylococcus aureus	3 (5.0%)	9 (9.8%)	0.52
Streptococcus pneumoniae	2 (3.3%)	1 (1.09%)	0.20
Streptococcus lugdonesis	0	2 (2.1%)	--
Staphylococcus capitis	1 (1.6%)	0	--
Staphylococcus hominis	0	9 (9.8%)	**0.02**
Staphylococcus haemolyticus	1 (1.6%)	3 (3.2%)	--
Gram negative organisms	**39 (65%)**	**48 (52.7%)**	0.13
Escherichia coli	18 (30%)	17 (18.6%)	0.31
Pseudomonas aeruginosa	7 (11.6%)	12 (13.1%)	0.42
Pseudomonas putidia	1 (3.3%)	0	--
Klebsiella pneumoniae	1 (3.3%)	6 (6.5%)	0.09
Acinetobacter species	5 (8.3%)	5 (5.4%)	0.72
Protues mirabilis	1 (3.3%)	0	--
Enterobacter species	1 (3.3%)	3 (3.2%)	0.41
Providencia stuartii	1 (3.3%)	0	--
Salmonella typhi	1 (3.3%)	0	--
Strenotrophomonas maltophilia	3 (5.0%)	2 (2.1%)	0.48
Haemophilus influenza	0	1 (1.09%)	--
Haemophilus parainfluenza	0	1 (1.09%)	--
Chryseomonas luteola	0	1 (1.09%)	--
	60 (39.7%)	**91 (60.3%)**	

Table-3: Resistance pattern of common used antibiotics against commonly isolated pathogens during calendar years 2003 and 2006

Microorganism	Antibiotics	Resistance in Year 2003	Resistance in Year 2006	*p*-value
St.epidermidis	Erythrocyn	9/10 (90%)	6/11 (54.5%)	0.07
	Methicillin	5/10 (50%)	4/5 (80%)	0.26
	Piperacillin/tazobactum	5/9 (55.6%)	2/11(18.2%)	0.08
	Vancomycin	0/10 (0%)	0/11 (0%)	--
St.aureus	Erythrocyn	1/3 (33.3%)	2/9 (22.2%)	0.70
	Methcillin	1/3 (33.3%)	2/6 (33.3%)	0.10
	Vancomycin	0/3 0%)	0/9 (0%)	--
Escherichia coli	Piperacillin/tazobactum	2/18 (11.1%)	2/17 (11.8%)	0.95
	Ceftriaxone	10/17(58.8%)	11/17 (64.7%)	0.72
	Imipenem	0/18 (0%)	0/17 (0%)	--
	Ciprofloxacin	16/18 (88.9%)	15/17 (88.2%)	0.95
	Amikacin	1/17 (5.6%)	0/17 (0%)	0.31
	Ceftazidine	10/17(58.8%)	11/17 (64.7%)	0.72
P.aeruginosa	Piperacillin/tazobactum	0/6 (0%)	1/12 (8.3%)	0.46
	Imipenem	0/7 (0%)	2/12 (16.7%)	0.25
	Ciprofloxacin	0/6 (0%)	6/12 (50%)	**0.03**
	Amikacin	0/7 (0%)	0/12 (0%)	--
	Ceftazidine	1/6 (16.7%)	1/12 (8.3%)	0.59
K.pneumoniae	Piperacillin/tazobactum	0/1 (0%)	0/6 (0%)	--
	Ceftriaxone	1/1 (100%)	4/6 (66.7%)	0.49
	Imipenem	0/1 (0%)	0/6 (0%)	--
	Ciprofloxacin	1/1 100%)	3/5 (60%)	0.43
	Amikacin	0/1 (0%)	0/6 (0%)	--
	Ceftazidine	0/1 (0%)	3/6 (50%)	0.35
Acinetobacter	Piperacillin/tazobactum	4/5 (80%)	3/ 4 (75%)	0.85
	Cefoperazone/sulbactm	--	0/4 (0%)	--
	Ceftriaxone	4/5 (80%)	4/5 (80%)	1.0
	Imipenem	4/5 (80%)	¾ (75%)	0.85
	Ciprofloxacin	4/5 (80%)	3/3 (100%)	0.40
	Ceftazidine	4/5 (80%)	4/4 (100%)	0.34

CONCLUSIONS

The present study shows the spectrum and antibiotic susceptibility patterns of pathogens in adult febrile neutropenic patients at our institute. Continuous surveillance of the spectrum of locally prevalent pathogens and their susceptibility patterns is essential for formulation of therapeutic regimens for chemotherapy induced febrile neutropenic patients.

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