Microbial Etiology of Febrile Neutropenia

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Abstract Bacterial and fungal infections are a major cause of morbidity and mortality among neutropenic patients. The choice of empiric antimicrobial regimen is based on susceptibility pattern of locally prevalent pathogens. From 64 febrile neutropenic patients with clinical sepsis, blood and other appropriate clinical specimens were processed to determine bacterial and fungal spectrum and their antimicrobial susceptibility pattern. Risk factors for developing sepsis were determined by case-control study. 68 organisms were recovered. Fifteen (22.05%) were Gram-positive cocci with predominance of methicillin Sensitive *S. aureus* (10.29%), 47 (69.11%) were Gram-negative rods with predominance of *Klebsiella pneumoniae* (30.88%) and four were Non albicans *Candida*. 81% and 60% of *Klebsiella* and *E. coli* were ESBL producers. All species of *Candida* were sensitive to amphoterecin B and voriconazole. Duration and extent of neutropenia, chemotherapy, immunosuppressive therapy, altered mucosal barriers and presence of central venous lines were statistically significant risk factors for developing sepsis. Gram-negative bacteria were the predominant isolates. The choice of therapy in neutropenic patients should be

formulated based on local spectrum of microbes and local and regional resistance patterns.

Keywords Febrile neutropenia · Infection · Aetiology · Risk factors

Introduction

Neutropenia is defined as an absolute neutrophil count (ANC) of less than or equal to 500 cells per mm³ or a count which is expected to fall to that level within the next 1–2 days [1]. It is a common complication in patients receiving immunosuppressive therapy for any cause such as those with acute leukemia and other hematological malignancies, after bone marrow transplantation and in aplastic anemia [2]. Infection is an important complication of neutropenia and is associated with a high morbidity and mortality. Common amongst these infections are those involving the blood stream and lower respiratory tract. In febrile neutropenic patients, the attack rate of blood stream infection (BSI) is reported to be between 11 and 38% [3].

Optimal management of established infection is mandatory to improve outcome in neutropenic patients. Globally, the spectrum of organisms associated with infections in neutropenic patients is showing a change with higher rates of resistant pathogens. From the predominant Gram-positive cocci of the 50s and 60s to the Gram-negative bacilli later, the emergence of multi drug resistant non fermenting aerobic rods in the 90s and a shift back to the Gram-positive cocci in the last two decades in some regions has created a problem of defining effective empiric therapy [4–7]. In trials conducted by The European Organisation for Research and Treatment of Cancer International Antimicrobial Therapy Cooperative Group (EORTC-IATCG) the frequency of

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Gram-positive isolates has been steadily increasing from 29% of single-organism bacteraemias between 1973 and 1976 to 41% between 1983 and 1986, 64% between 1986 and 1988, 67% between 1991 and 1992, and 69% between 1993 and 1994. In these same trials, the rate of single-agent Gram-negative bacteraemias dropped from 71 to 31% [8, 9]. With the changing flora and susceptibility pattern to antibiotics, the choice of empiric therapy has become problematic and must be evaluated on the basis of local patterns of infectious agents and local and regional resistance patterns. Ours is a tertiary care multi-speciality large teaching hospital with a hematology unit. The present study was conducted on hematology patients with suspected sepsis to determine the microbial spectrum of infections, the resistance pattern of the isolates and the risk factors that predispose to the development of infections.

Material and Methods

A prospective study was carried out in the department of microbiology in collaboration with the department of clinical hematology over a period of 9 months in 2006. All patients admitted to the hematology ward during the study period, suspected of clinical sepsis were included. Clinical sepsis was defined as per the criteria established by American College of Physicians and Society of Critical Care Medicine (ACOM & SCCM) which included temperature $>38^{\circ}\text{C}$, heart rate $>90/\text{min}$ and respiratory rate $>20/\text{min}$ [10]. Neutropenia was defined as an ANC of $500/\text{mm}^3$ or less or a count that is expected to fall to that level in the next 1–2 days [1].

Blood and other appropriate specimens were collected for culture. The specimens were processed for bacteria and fungi as per standard protocol. Identification of bacterial and fungal isolates was done as per routine standard microbiological methods. Antimicrobial susceptibility testing of bacterial isolates was performed by the Kirby Bauer Disk Diffusion method as per CLSI guidelines [11]. The antimicrobials tested included AM—Ampicillin (10 μg), RC—Ciprofloxacin (5 μg), GM—Gentamicin (10 μg), PT—piperacillin + tazobactam (100/10 μg), IM—Imipenem (10 μg), AK—Amikacin (30 μg), AG—Coamoxyclav (20/10 μg), CB—Cefuroxime (30 μg), CF—Cefotaxime (30 μg), Rp—Ceftriaxone (30 μg), MP—Meropenam (10 μg), CM—Cefoperazone + sulbactam (30/10 μg), DC—Sparfloxacin (5 μg), NT—Netilmicin (30 μg), CPM—Cefepime (30 μg), PG—Penicillin G (10 units), OC—Oxacillin (1 μg), VA—Vancomycin (30 μg), ER—Erythromycin (15 μg), CO—Cotrimaxazole (1.25 $\mu\text{g}/23.75$), CZ—Cefazolin (30 μg), CD—Clindamycin (2 μg), LZ—Linezolid (30 μg), and TEC—Teicoplanin (30 μg). ESBL production was detected by CLSI reference method and Jarlier's double disk synergy method [11, 12]. Antifungal

susceptibility testing was performed against fluconazole, voriconazole and amphoterecin B by microbroth tube dilution method as per CLSI guidelines [13]. For fluconazole, concentrations ranging from 0.0313 to 64 $\mu\text{g}/\text{ml}$ in doubling concentrations were tested. For voriconazole and amphoterecin B, concentrations ranging from 0.0313 to 16 $\mu\text{g}/\text{ml}$ in doubling concentrations were tested. Clinical details of the patients and results of total and differential WBC counts were recorded.

A case control study was carried out for determining the risk factors for developing sepsis. Controls were patients admitted in the same ward during the same period but without evidence of sepsis. Equal number of cases and controls were included. Results were noted and data was analysed by using SPSS for windows version 10.0. Student's two-tailed *t*-test was used for quantitative variables. Differences between group proportions were assessed with χ^2 -test or for small numbers Fisher's exact test. Potential risk factors were analyzed by using univariate method. For risk factor analysis *p* value and likelihood ratio were calculated. *P* < 0.05 was considered significant.

Results

During the study period, there were 71 clinically suspected cases of sepsis. Of these, 64 had febrile neutropenia. Incidence of febrile neutropenia was maximum in patients with leukemia (53.5%, 23/43) and aplastic anemia (53.3%, 24/45) followed by lymphoma (50%, 4/8), myelodysplastic syndrome (36.3%, 4/11) and hypoplastic anemia (29.1%, 7/24). A total of 165 specimens which included 113 blood cultures, 17 sputa, 17 Urine, 6 Pus, 1 BAL and 1 throat swab, were processed. 68 isolates were obtained from 29 culture positive febrile neutropenic patients (Table 1). 69% of the isolates were Gram-negative bacilli. *Klebsiella pneumoniae* was the predominant isolate followed by *E. coli* and *S. aureus*. Six fungal isolates were recovered, four from blood and two from urine. Five of these were *Candida* spp. 36.2% of blood cultures were positive for bacterial or fungal growth.

The antimicrobial susceptibility pattern revealed a high level of resistance to routinely used antimicrobials including third generation cephalosporins and quinolones. (Tables 2, 3) The Enterobacteriaceae were maximally sensitive to carbapenems (100%) followed by amikacin and betalactam betalactamase inhibitor combinations (BLBLI). Amongst the BLBLI, PT demonstrated a better sensitivity as compared to CM. Their susceptibility to cefepime (fourth generation cephalosporin) was lower than that to BLBLI. 81% of *Klebsiella* and 60% of *E. coli* were ESBL producers. Sparfloxacin demonstrated a better sensitivity as compared to ciprofloxacin. The sensitivity of *Acinetobacter* spp.

Table 1 Distribution of bacterial and fungal isolates ($n = 68$)

Organism isolated	Blood	Sputum	Urine	Pus	Throat swab	BAL	Total
Gram-positive isolates	11	1	1	1	1	0	15 (22.05%)
<i>Staphylococcus aureus</i>	6	–	–	1	–	–	7 (10.29%)
<i>Staphylococcus hemolyticus</i>	4	–	–	–	–	–	4 (5.88%)
<i>Enterococcus faecalis</i>	1	1	1	–	–	–	3 (4.41%)
<i>Streptococcus pyogenes</i>	–	–	–	–	1	–	1 (1.47%)
Gram-negative isolates	26	13	3	4	0	1	47 (69.11%)
<i>Klebsiella pneumoniae</i>	8	10	–	2	–	1	21 (30.88%)
<i>Escherichia coli</i>	6	1	3	–	–	–	10 (14.7%)
<i>Acinetobacter baumannii</i>	2	2	–	–	–	–	4 (5.88%)
<i>Acinetobacter hemolyticus</i>	3	–	–	–	–	–	3 (4.41%)
<i>Acinetobacter</i> spp.	1	–	–	–	–	–	1 (1.47%)
<i>Pseudomonas aeruginosa</i>	3	–	–	2	–	–	5 (7.35%)
<i>Salmonella</i> group B	2	–	–	–	–	–	2 (2.94%)
<i>Enterobacter aerogenes</i>	1	–	–	–	–	–	1 (1.47%)
Fungi	4	0	2	0	0	0	6 (8.82%)
<i>Candida albicans</i>	–	–	2	–	–	–	2 (2.94%)
<i>Candida tropicalis</i>	2	–	–	–	–	–	2 (2.94%)
<i>Candida krusei</i>	1	–	–	–	–	–	1 (1.47%)
<i>Aspergillus niger</i>	1	–	–	–	–	–	1 (1.47%)
Total	41	14	6	5	1	1	68 (100%)

Table 2 Antimicrobial susceptibility pattern of Gram-negative isolates ($n = 47$), % sensitive

Organism	AM	AG	CB	CF	RP	FG	RC	DC	GM	AK	NT	IM	MP	PT	CM	CPM
<i>Klebsiella pneumoniae</i> ($n = 21$)	0	4.76	4.76	4.76	4.76	19	28.5	76.1	19	85.7	71.4	100	100	95.2	80.9	76.1
<i>Escherichia coli</i> ($n = 10$)	20	40	20	30	20	40	40	100	50	80	100	100	100	100	90	80
<i>Salmonella</i> group B ($n = 2$)	100	100	100	100	100	–	100	–	100	100	–	–	–	–	–	100
<i>Enterobacter</i> spp. ($n = 1$)	0	0	100	100	100	100	100	100	100	100	100	100	100	100	100	100
<i>Acinetobacter baumannii</i> ($n = 4$)	25	25	25	25	50	75	50	75	50	50	75	100	100	75	50	75
<i>Acinetobacter hemolyticus</i> ($n = 3$)	33	33	67	67	67	100	33	67	67	67	100	100	100	100	67	67
<i>Acinetobacter</i> spp. ($n = 1$)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
<i>Pseudomonas aeruginosa</i> ($n = 5$)	–	–	–	0	0	60	60	80	40	60	60	80	80	80	40	40
Overall	16.7	23.8	23.8	26.2	26.2	38.1	40.5	78.6	40.5	81	76.2	95.2	95.2	90.5	76.2	78.6

and *Pseudomonas aeruginosa* to carbapenems was 100 and 88%, respectively. Amongst the aminoglycosides, netilmycin had a better sensitivity as compared to gentamicin and amikacin. All *Staphylococcus aureus* isolates were methicillin sensitive while one isolate of *Staphylococcus hemolyticus* was methicillin resistant. All enterococcal isolates were sensitive to vancomycin and showed low level resistance to gentamicin. All species of *Candida* were sensitive to amphoterecin B and voriconazole (Table 4). One strain of *Candida tropicalis* showed dose dependant sensitivity while one strain of *Candida krusei* showed resistance to fluconazole.

An analysis of the duration of neutropenia with sepsis in the 64 patients revealed that, 15.62% had a duration of less than 4 days, 31.25% a duration of 4–6 days, 23.44% a duration of 7–10 days and 29.69% a duration of more than 10 days. 84.38% patients developed sepsis if duration of neutropenia was >4 days.

Also, 49 had counts less than 200 of whom 38 had counts less than 100. 92.11% of patients with counts less than 100 had clinical evidence of sepsis. Risk factor analysis (Table 5) revealed neutropenia as the major risk factor for development of sepsis ($P = 9.19 \times 10^{-5}$). Chemotherapy, immunosuppressive therapy, patients with

Table 3 Antimicrobial susceptibility pattern of Gram-positive isolates ($n = 14$), % sensitive

Organism	PG	OC	RC	GM	VA	ER	CO	CZ	AG	NT	DC	CD	LZ	TEC
<i>Staphylococcus aureus</i> ($n = 7$)	0	7	0	7	7	4	0	6	7	–	–	–	–	–
<i>Staphylococcus hemolyticus</i> ($n = 4$)	2	3	2	3	4	1	1	3	3	4	4	4	4	4
<i>Enterococcus</i> spp. ($n = 3$)	3		2	0	3	2	0	–	–	–	–	–	3	3
<i>Streptococcus pyogenes</i> ($n = 1$)	1		1	0	1	1	0	–	–	–	–	–	1	1

Table 4 Antifungal susceptibility pattern of fungal isolates ($n = 6$)

Species	Amphoterecin B		Voriconazole		Fluconazole		
	Sensitive MIC < 1	Resistant MIC ≥ 1	Sensitive MIC < 1	Resistant MIC ≥ 4	Sensitive MIC ≥ 8	Dose dependant sensitive MIC 16–32	Resistant MIC ≥ 64
<i>C. albicans</i> ($n = 2$)	2	–	2	–	2	–	–
<i>C. tropicalis</i> ($n = 2$)	2	–	2	–	1	1	–
<i>C. krusei</i> ($n = 1$)	1	–	1	–	–	–	1
<i>A. niger</i> ($n = 1$)	1	–	1	–	–	–	–

MIC minimum inhibitory concentration in $\mu\text{g/ml}$

altered mucosal barrier, presence of central venous lines, duration of neutropenia of more than 4 days ($P = 0.021$) and a mean duration of hospitalization of 23.87 days ($P = 1.05 \times 10^{-5}$) were other important risk factors for developing sepsis. Risk factors for the development of fungal sepsis were an ANC of less than 100 ($P = 0.044$), increased length of hospital stay ($P = 0.002$), prolonged immunosuppressive therapy ($P = 0.021$) and prolonged antibiotic therapy ($P = 0.032$).

Thirteen patients out of 64 expired. Among these, five had an ANC of less than 100.

Discussion

The present study on microbial aetiology of febrile neutropenia in clinically suspected cases of sepsis included 64 patients. Blood cultures were processed for all these patients. Specimens from other sites were collected when infection was suspected at these sites.

Of the 68 isolates recovered, 41 were from blood cultures and 27 were from other sites. Bacteria accounted for 91.1% (62/68) of the total isolates while 8.9% (6/68) were fungal. 75.8% (47/62) of bacterial isolates were Gram-negative bacilli while 24.2% (15/62) were Gram-positive cocci indicating a predominance of infections due to Gram-negative organisms. These results are similar to those reported in literature [14]. A changing trend from Gram-negative to Gram-positive organisms over the last two decades has been observed in some studies reported in literature especially those from the developed countries [4–7]. This change has been attributed to many factors such as widespread use of

indwelling central venous access devices, use of intensive chemotherapy toxic to upper and lower gastrointestinal mucosa, use of quinolone based antibacterial chemoprophylaxis that suppresses the aerobic Gram-negative bacilli colonizing the gastrointestinal tract but fails to suppress the microaerophilic Gram-positive cocci and the use of histamine H2 receptors blockers, which reduce gastric pH and promote overgrowth of oropharyngeal Gram-positive microflora [15]. In our haematology unit, quinolones are not used for routine prophylaxis and there is restricted use of long term indwelling venous catheters. Most patients however depending on their primary diagnosis receive h2 receptor blockers, intensive chemotherapy, and indwelling venous catheter. According to Pizzo et al., the Gram-positive trend has not been predominant in the developing world [16]. In developing countries, Gram-negative organisms including *Klebsiella* species, *E. coli* and *Pseudomonas aeruginosa*, still predominate with a pattern of infection similar to that in US and Europe of the 1960s and 1970s. It has also been observed that Gram-negative bacilli are still the predominant infectious agents in those centers where quinolone prophylaxis is not a routine procedure [17]. Gaytan-Martinez et al. [18] have reported *E. coli* as the most frequently isolated agent of primary bacteremia in febrile neutropenic patients. At Hacettepe University Medical Faculty, Turkey, the first three infecting agents in febrile neutropenic patients over the last 10 years have been *E. coli*, *Enterobacter* spp. and *Pseudomonas aeruginosa* [14]. These findings are consistent with the findings of the present study.

The present study also analysed the sensitivity pattern of the bacterial and fungal isolates recovered. Globally, there has been a significant increase in the resistance profile of

Table 5 Risk factors for developing sepsis

Risk factor	Number who developed sepsis (n = 71)	Number who did not develop sepsis (n = 71)	P value	Likelihood ratio	Significance
<i>Neutropenia</i>					
Yes	64 (90.1%)	9 (12.7%)	9.19×10^{-15}	6.81×10^{-23}	Significant
No	7 (9.90%)	62 (87.3%)			
<i>Present chemotherapy</i>					
Yes	26 (36.6%)	13 (18.3%)	0.023	0.014	Significant
No	45 (63.4%)	58 (81.7%)			
<i>Mucosal barrier injury</i>					
Yes	25 (35.2%)	13 (18.3%)	0.036	0.022	Significant
No	46 (64.8%)	58 (81.7%)			
<i>Presence of central line</i>					
Yes	24 (33.8%)	4 (5.6%)	3.32×10^{-05}	1.07×10^{-05}	Significant
No	47 (66.2%)	67 (94.4%)			
<i>History of immunosuppressive therapy</i>					
Yes	21 (29.6%)	11 (15.5%)	0.05	0.043	Significant
No	50 (70.4%)	60 (84.5%)			
<i>H/o bone marrow puncture</i>					
Yes	67 (94.4%)	58 (67.6%)	6.86×10^{-05}	2.29×10^{-05}	Significant
No	4 (5.6%)	23 (32.4%)			
<i>Past H/o hospitalization</i>					
Yes	37 (52.1%)	41 (57.7%)	0.613	0.5	Not significant
No	34 (47.9%)	30 (42.3%)			
<i>Past H/o chemotherapy</i>					
Yes	14 (19.7%)	09 (12.7%)	0.363	0.253	Not significant
No	57 (80.3%)	62 (87.3%)			
<i>H/o blood transfusion</i>					
Yes	36 (50.7%)	35 (49.3%)	1	0.867	Not significant
No	35 (49.3%)	36 (50.7%)			

clinical isolates including those recovered from febrile neutropenic patients [19–22]. In the present study, majority of the Gram-negative isolates were multidrug resistant with high prevalence of ESBL producing *E. coli* and *Klebsiella* strains. Two published studies from Pakistan, on antimicrobial resistance in bacterial isolates from febrile neutropenic patients have highlighted an increase in the resistance to most of the commonly used drugs including third generation cephalosporins particularly in Enterobacteriaceae and multidrug resistant *Acinetobacter* species [19, 20].

According to guidelines published by Infectious Disease Society of America (IDSA 2002), initial therapy in febrile neutropenic patients consists of monotherapy with one of the third generation cephalosporins or carbapenams or a combination therapy with an aminoglycoside with third generation cephalosporin. Intravenous vancomycin is to be limited to catheter related sepsis [23]. The in vitro susceptibility testing results of the present study indicate that third generation cephalosporins would not be of clinical use in these patients

though amikacin may prove to be useful. A combination of amikacin with piperacillin + tazobactam maybe recommended for initial empirical antibiotic therapy in febrile neutropenic patients who develop infection. The current empirical therapy followed in this institute is a combination of amikacin with cefepime or piperacillin + tazobactam. It would be more prudent not to use cefepime which has a lower sensitivity compared to piperacillin + tazobactam. About 35% patients required change in empirical line of antibiotic treatment depending on culture sensitivity report. To the increasing demands for the use of vancomycin as initial empiric therapy, it can be stated that addition of glycopeptides for initial empirical therapy in this institute is not recommended presently, due to the very low prevalence of methicillin resistant isolates.

Amongst the fungal isolates, non-albicans candida spp. were predominant. The frequency of association of *Candida* spp. especially the non-albicans candida as causative agents of BSI is on the rise world over. In a study conducted by

Pasqualotto et al. [23], species other than *C. albicans* were responsible for 51.8% of the candidemias. These included mainly *C. parapsilosis* (21.7%), and *C. tropicalis* (13.3%). *C. glabrata* and *C. krusei* were infrequent (3.6% each) [24]. Chakrabarti and Shivprakash [24] have reported an overall increase in non-albicans candida species as both colonizers and pathogens causing fungal blood stream infections [25]. Antifungal prophylaxis is indicated in those settings with a higher prevalence of fungal infections. Antifungal treatment is initiated on signs of superficial or invasive fungal infections or if fever is persistent after 3–5 days of antibiotics [23].

One of the objectives of the present study was to determine the risk factors for developing sepsis using a case control study. Neutropenia (ANC less than 500 cells/cm) was the most significant risk factor for developing sepsis (P value = 9.19×10^{-15}). Pagano et al. have also found neutropenia as a significant risk factor for developing sepsis [26]. Various studies have shown that most infections occur when neutrophil count falls below 500 and the risk increases when it falls below 100 and approaches to zero [1, 2, 27, 28]. In this study also, it was found that the incidence of sepsis was more (88.9%) when ANC was below 500 and a greater proportion of patients (92.11%) patients developed sepsis when ANC was less than 100. Duration of neutropenia was also found to be a significant risk factor for developing sepsis with 84.38% of patients developing sepsis when duration of neutropenia was more than 4 days. These findings are consistent with those reported in literature [26, 29]. The other significant risk factors identified in the present study were altered mucosal barriers and presence of central line. Chemotherapy induced injury to oral and gastrointestinal mucosa has been reported to significantly increase infections and morbidity in FN patients [30, 31]. Central venous catheters and intravascular devices are known to be significant risk factors for BSI. In the current study, presence of a CVC/IVC was found to be a significant risk factor for BSI in FN patients, and this finding is similar to that reported in literature [26, 27, 32].

Mortality among patients who developed sepsis was 18.3% as compared to 8.5% among patients who did not develop sepsis.

Conclusions

With the changing flora and susceptibility pattern to antibiotics, guidelines as to ‘best therapy’ of infections in neutropenic patients must be evaluated on the basis of local patterns of infections and local and regional resistance pattern. In contrast to other studies abroad, Gram-negative organisms were the predominant isolates. Non-albicans candida were the predominant fungal isolates. Duration and extent of neutropenia were important risk factors for developing sepsis.

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