Response of First-Line Antibiotic Therapy in Patients with Febrile Neutropenia During Treatment of Hematological Disorders

M. Taj · R. N. Qureshi · T. Farzana ·
T. S. Shamsi · S. S. Ahmed

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Abstract Patients with hematological disorders develop febrile neutropenia (FN); most of these events remain undetermined in origin. We performed a prospective study to determine the microbiological characteristics of infections and their response to the first-line antibiotic therapy in FN. The study was conducted at National Institute of Blood Disease and Bone Marrow Transplant. Two-hundred episodes of FN were assessed for the bacterial growth, antimicrobial susceptibility pattern and response to the first-line treatment of FN. All patients were given Ceftazidime and Amikacin Bosch Pharmaceutical (Pvt. Ltd), as first-line antibiotic in FN. Out of 200 episodes we had 108 clinically and microbiologically documented infections. The isolated frequencies for gram negative and gram positive organisms were $n = 52$ and 49 (48 and 45 %) respectively. Among gram negative micro-organisms, *Escherichia coli* (*E. coli*) was isolated in 15 (28.8 %), *Klebsiella pneumoniae* in 4 (7.6 %) and *Pseudomonas aeruginosa* in 10 (19.2 %) were in highest frequencies.

Methicillin sensitive staphylococci emerged as the frequently isolated gram-positive bacteria. Eight-one episodes (45.3 %) responded to the first-line treatment and death reported in 20 cases (10 %). Our study showed almost equal trend of gram positive and gram negative bacteria isolated from patients suffering from neutropenic fever. Empirical use of Ceftazidime and Amikacin as first-line antibiotics was able to cover the infection only in 45.3 % of episodes suffering from FN.

Introduction

Febrile neutropenia (FN) is a medical emergency and still considered to be a major cause of morbidity and mortality in the treatment of hematological disorders. Fever in neutropenic patient is defined as a temperature $>38.3^{\circ}\text{C}$ (101°F), or a sustained temperature $>38.0^{\circ}\text{C}$ (100.4°F) for more than 1 h. Neutropenia is defined as an absolute neutrophil count (ANC) <500 cells/ mm^3 , or $<1,000$ cells/ mm^3 with a predicted nadir of <500 cells/ mm^3 [1–3].

Infectious etiology is identified in only 30 % of the episodes and bacteremia is the most frequently type of infection in 25 % of patients [4]. In general 80 % of the identified infections arise from patient's endogenous flora. In early 1950s, *Staphylococcus aureus* was the most frequent organism identified in these patients [6]. Later the pattern was replaced by gram-negative bacilli and *Escherichia coli*, *Klebsiella* species and *Pseudomonas aeruginosa*, emerged as most commonly identified pathogens until the 1980s. In USA two surveys done in 1995 and 2000 for infections in neutropenic patients and reported gram positive organisms accounting for 62 and 76 % while gram negative organisms accounted for 22 and 14 % of all blood stream infections [7]. Number of factors accounted for this

M. Taj (✉) · R. N. Qureshi · T. Farzana ·
T. S. Shamsi · S. S. Ahmed

Department of Hematology and Oncology, National Institute of
Blood Disease & Bone Marrow Transplantation, ST 2/A Block
17 Gulshan-e-Iqbal, Sir Shah Suleman Road, KDA Scheme 24,
Karachi, Pakistan
e-mail: mehwishfaisal@gmail.com

R. N. Qureshi
e-mail: drrizwannabi@gmail.com

T. Farzana
e-mail: drtasneemfarzana@gmail.com

T. S. Shamsi
e-mail: shamsi@super.net.pk

S. S. Ahmed
e-mail: Sajjad-micro@hotmail.com

trend which included indwelling catheters, broad spectrum cover for *P. aeruginosa* and gram negative infections [4]. The use of broad spectrum antibiotics has resulted in emergence of multi-drug resistant gram negative and gram positive organisms. Hence the selection of first-line cover should vary according to the local prevalence of micro-organisms and their culture sensitivity pattern.

This alarming emergence of resistant micro-organisms is of great concern particularly for our resource limited country where the cost of cancer chemotherapy becomes almost doubled due to such offending organisms encountered in neutropenic phase leading to overall poor prognoses. Previous data published in 2003 and 2006 by same institute highlighted the frequency of these micro-organism and their culture and sensitivity pattern [8]. We prospectively studied 200 episodes of FN managed as a complication of treatment of various hematological disorders.

Materials and Methods

The study was conducted prospectively at National Institute of Blood Diseases and Bone Marrow Transplant, Karachi. The characteristics of 200 episodes of febrile neutropenia in 125 patients secondary to hematological malignancies or its treatment. Patient's baseline characters and other relevant details of febrile neutropenia episode were documented from July 2007 to June 2008. Patients were eligible if they had a single measurement of oral temperature 38.5 °C (100 °F) or 38.0 °C on two or more occasions within 12 h, and the fever was not related to the administration of blood products or known pyrogenic substances [9].

All patients were evaluated by thorough routine general physical examination. Blood cultures were taken from a central or a peripheral vein before antibiotic initiation and with 48 h interval or thereafter during persistent fever until culture results became negative. Bacterial blood-stream infection was defined as the presence of clinical symptoms in association with one, of a set of two, positive cultures when the isolated pathogen was a gram-negative agent or associated with two or more positive blood cultures when the pathogen isolated was a gram-positive agent [10]. Additionally, cultures from urine samples and throat swab, if appropriate, from other suspected body sites were obtained. All patients were evaluated by a complete blood count and standard blood chemistry. Patients having fever due to non-infectious cause e.g., transfusion reaction, drug reaction or other known pyrogenic substances were excluded from the study.

Febrile neutropenia was managed according to IDSA guidelines [1]. The instituted antibiotics were ceftazidime 50 mg/kg IV 8 hourly and amikacin 15 mg/kg IV 12 hourly

along with other supportive care measures. The success of antibiotic therapy was defined as no fever for 3 successive days and the absence of clinical signs/the eradication of an identified pathogen. If no response after 48 h, ceftazidime was switched to carbapenem group. Vancomycin or teicoplanin were added if indwelling catheter infection was suspected or as additional requirement of gram positive cover. Repeated cultures were sent in cases of fever unresponsive to therapy. The death of a patient during treatment was not considered to be a treatment failure.

Febrile episodes were classified according to the kind of infection as (i) Pyrexia of unknown origin (PUO); (ii) microbiologically documented infection (MDI); (iii) clinically documented infection (CDI); according to the suspected source or site of infection. PUO was defined as both the absence of any clinical or radiological sign of infection other than fever without isolation of causative organism [11].

Data were gathered in compliance with the principles of the Declaration of Helsinki and then anonymized. No patient consent was needed because of the confidential nature of this study, which was approved by the institutional review board of NIBD. Blood cultures were performed at NIBD&BMT lab using standard methods [10]. Maximum incubation time for negative cultures was 7 days. The identification of isolates involved standard microbiological procedures.

Statistical Analysis

All data are described as mean $\pm$ SD. Continuous variables were compared using the independent-samples *t* test and categorical variables were compared using the Chi square test or Fisher's exact test for association. Differences were considered statistically significant when $P < 0.05$. Data were analyzed by statistical software (SPSS for Windows 17.0; SPSS, Chicago, IL).

Results

Overall, 200 infectious episodes occurred in 125 patients, 85 (68 %) were females; median age was 24.43 ± 17.26 years (range 1–70). Table 1 summarizes the demographic data for the patients with febrile neutropenia included in the study. Table 2 showed List of Bacteria that caused disease in neutropenic patients, with their sites of infections. The frequency of microbiologically documented infections (MDI) accounted for 54 % while clinically documented infections (CDI) were 34 %, in which pneumonia was found the commonest infection (25 %) followed by gastrointestinal infections (17 %). No source of infection could have been found in 12 % of cases and reported

Table 1 Characteristics of the 200 patients with episode of febrile neutropenia

Total episodes	No = 200	(%)
Gender		
Male	40	32
Female	85	68
Age (median and range)	24.43 ± 17.26 (1–70)	
Microbiologically documented infections (MDI)	108	54
Clinically documented infections (CDI)	68	34
Pyrexia of undetermined origin (PUO)	24	12
Diagnosis		
ALL	83	41.5
AML	41	20.5
APML	3	1.5
HCL	2	1
MDS	5	2.5
CLL	12	6
NHL	4	2
FHLH	1	0.5
WM	1	0.5
AA	34	18
Post-BMT	14	7
Mean duration of fever (day; mean ± SD, range)	11 ± 7.5 (3–20)	
Mean duration of antibiotic treatment (day; mean + SD; range)	15.6 ± 7.6 (5–46)	
Death	20	10

AA Aplastic anemia, ALL Acute lymphoblastic leukemia, AML Acute myeloid leukemia, APML Acute promyelocytic leukemia, CLL Chronic lymphocytic leukemia, FHLH, HCL Hairy cell leukemia, NHL Non-Hodgkin lymphoma, Post-BMT Post bone marrow transplant, WM Waldenstrom macroglobulinemia

as pyrexia of undetermined origin (PUO). Mean duration of fever (day; mean ± SD, range) reported as 11 ± 7.5 (3–20), while mean duration of antibiotic treatment (day; mean + SD; range) recorded as 15.6 ± 7.6 (5–46) and death was reported in 20 (10 %). Table 3 shows infectious complications identified during the study period.

Table 4 shows 108 (54 %) microbiologically documented infectious episodes (MDI) of total 200 febrile episodes. Table 5 shows the sensitivity data of gram-positive and gram-negative micro-organisms. Gram negative microorganisms were isolated in 48 % of samples while gram positive isolated in 45.3 %. *E. coli* and *P. aeruginosa* were found in highest frequency among gram negative organisms [28.8 % ($n = 15$) and 19.2 % ($n = 10$)] respectively. *E. coli* showed only 33 % sensitivity to ceftazidime while 86 % to amikacin (the first-line antibiotics used in our institution as febrile neutropenia

Table 2 List of bacteria that caused disease in neutropenic patients, with their sites of infections

Organisms	Site of Infection
Gram-positive bacteria	
<i>Staph aureus</i>	Blood/catheter
Coagulase negative staphylococci	Blood/Catheter
Viridans group streptococci	Blood/Catheter
Gram-negative bacteria	
<i>P. aeruginosa</i>	Blood/Catheter
	Throat/sputum
<i>Escherichia coli</i>	Blood/sputum
	Urine
<i>Klebsiella</i> species	Blood/sputum
	Urine/pus
<i>Enterococcus</i> Species	Blood/Catheter
	Urine

Table 3 Infectious complications identified during the study period

Site of infection	Number (%)
Microbiologically documented infections (MDI)	108 (54)
Blood cultures	56.5
Urine cultures	15.5
Throat cultures	15.6
Stool cultures	10.1
Fever of unknown origin	12
Clinically documented infections (CDI) (including X-ray & ultrasound)	68 (34)
Pneumonia	25
Soft tissue infections	13
Mucositis	7
Thrombophlebitis or line-related infection	10
Urinary tract infections	15.5
GIT infections	17
Perianal infections	10
Total	200 (100)

protocol) while sensitivity to tazobactam-piperacillin was 85 % and was 91 % for carbapenem group.

P. aeruginosa was found 70 % sensitive to the ceftazidime and 90 % sensitive to amikacin while 95 % sensitive to tazobactam and carbapenem. Hence cephalosporin group showed considerable resistance for *E. coli* and *P. aeruginosa*. Quinolones sensitivity pattern for *E. coli* and *P. aeruginosa* was and 33 % respectively.

Table 4 Microbiologically documented infectious episodes (MDI), $n = 108$ (54 %)

Gram negative organisms	$N = 52$	48.1 %	Gram positive organisms	$N = 49$	45.3 %
<i>E. coli</i>	15	28.8	Staph Aureus	18	30.66
<i>Bacillus</i> spp	3	5.76	MRSA	6	12.2
<i>Klebseilla pneumoniae</i>	4	7.69	Coagulase Negative staph	5	10.20
<i>Klebseilla</i> spp.	2	3.84	Bacilli	4	8.16
Enterobacter	2	3.84	Strep. Pneumoniae	6	12.24
Gram -ve cocci species	2	3.84	Strep. Viridins	4	8.16
Serratia	1	1.92	Enterococci	4	8.16
<i>Proteus mirabilis</i>	1	1.92	Beta Hemolytic Strep	2	4.08
<i>Pseudomonas aerigonsa</i>	10	19.2	Streptococcus Spp	3	6.12
<i>Pseudomonas</i> spp	7	13.46			
<i>Salmonella dysentriae</i>	2	3.84			
<i>Salmonella</i> Spp.	2	3.84			
<i>Salmonella para</i>	1	1.92			
Total	52		Total	49	

Table 5 Sensitivity data of Gram-positive and Gram-negative micro-organisms

Pathogens by type and class reference	Percentage of isolates susceptible, by drug										
	PITZ	CFT	CFX	CEF	CFZ	GNT	CIP	VAN	AMK	IMP	TEIC
Gram positive organisms											
MSSA (15)	20	–	–	–	40	–	40	100	86	–	100
MRSA (6)	50	–	–	–	50	50	–	83	50	–	83
Coagulase-negative staph (5)	80	80	–	–	75	80	80	100	80	–	100
Gram positive bacilli (4)	50	75	75	75	75	–	–	–	100	–	100
<i>Strep. pneumoniae</i> (6)	100	100	100	100	100	100	100	66	100	100	50
<i>Strep. viridins</i> (4)	100	75	75	75	75	50	50	50	100	100	50
<i>Enterococcus</i> species(4)	75	25	25	25	50	50	50	75	50	50	75
β -Hemolytic streptococci (2)	100	50	50	50	100	50	100	–	50	–	50
<i>Strep. Spp.</i> (2)	100	50	50	50	100	50	50	100	50	–	50
Gram negative organisms											
<i>Bacillus</i> Spp. (3)	100	100	100	33	100	66	100	–	100	100	–
Gram -ve cocci Spp (2)	100	50	100	100	–	100	100	–	50	100	–
<i>Escherichia coli</i> (15)	86	33	20	26	93	40	53	–	86	93	–
<i>Klebsiella pneumoniae</i> (8)	87	50	50	50	100	25	50	87	87	100	–
<i>Klebsiella</i> spp. (2)	100	50	50	100	100	–	100	50	50	100	–
<i>Enterobacter</i> spp (2)	–	100	100	100	50	100	100	100	100	100	100
<i>Serratia</i> spp. (1)	100	100	100	100	100	100	100	–	–	100	–
<i>Pseudomonas auroginosa</i> (10)	80	20	20	30	80	40	80	–	80	80	–
<i>Pseudo.</i> spp. (7)	85	85	85	57	85	71	14	–	–	71	–
<i>Proteus.</i> spp (3)	100	100	100	100	100	100	–	–	100	100	100
<i>Salmonella typhi</i> (4)	100	100	75	100	100	50	–	–	50	100	50
<i>Salmonella</i> spp (2)	100	50	50	100	100	50	–	–	50	100	50
<i>Salmonella paratyphi</i> (2)	100	50	100	100	100	–	100	–	100	100	50
<i>Bacteroids</i> spp (2)	100	100	100	100	50	–	100	–	50	50	50

Susceptibility rates were calculated based on NCCLS interpretive criteria

PITZ Piperacillin-tazobactam, CFT Ceftazidime, CFX Cefixime, CEF Ceftriaxone, CFZ Cefoperazone-sulbactam, GNT Gentamycin, CIP Ciprofloxacin, VC Vancomycin, AMK Amikacin, IMP Imipenem, TEIC Teicoplanin

S. Aureus was most frequently isolated gram positive microorganisms (42.8 %, $n = 21$) out of which 6 cases were reported as MRSA, showing 85 % sensitivity to vancomycin and 83 % to teicoplanin. There were five cases of coagulase-negative staphylococci (CoNS) which were sensitive to vancomycin and teicoplanin while 6 were Methicillin resistant Staphylococci (MRSA). Out of four cases of enterococci, one was vancomycin resistant (VRE). Four cultures were positive for fungal isolates (one candida albicans, one non-albicans candida and two aspergillus species), out of which three had evidence of invasive fungal infection. In our institution the first-line antibiotic treatment for febrile neutropenia was ceftazidime and amikacin till 2008 and response rate documented was 45.3 % in 200 episodes. On the basis of these findings the first line antibiotic was changed to tazobactam-piperacillin and amikacin. Among 200 episodes 18.9 % ($n = 17$) had prolonged neutropenia while 24.4 % (22) had multiple organisms in their cultures. Total 20 deaths were reported and mostly had either prolonged neutropenia or uncontrolled disease. Only two patients died of multi-organ failure and had multiple organisms isolated.

Discussion

Febrile neutropenia is one of the medical emergencies in the treatment of hematological malignancies. It is one of the most important factors contributing the overall outcome of any kind of chemotherapy regimen and hence requires very prompt intervention [1]. In this study 54 % cases of MDI, 34 % cases of CDI and 12 % cases of PUO, that is comparable to previous local data (54.3, 15.7 and 31 % respectively).

The prevalence of gram positive organisms was high 30 years back. Later the paradigm shifted to gram negative organism in last two decade. However various epidemiological studies in developed countries showed resurgence of gram positive infections in last decade, which was attributed to the use of intravenous catheter devices (IVCs) and use of anti-bacteria prophylaxis targeting gram negative organisms [8, 11].

The study showed an almost equal trend of infections with gram negative and gram positive micro-organisms. Intravenous catheter devices were present in 70 % of patients anti-bacterial prophylaxis was not used routinely.

The gram negative infections are frequently reported from the developing world [4]. European data from some centers shows the re-emergence of gram negative bacilli as dominant pathogen in the etiology of febrile neutropenia [11, 12]. Gram negative and gram positive infection frequencies were 48 and 45 % respectively in this study. In 2006 the percentage of infections with gram negative and

gram positive bacteria were 17.5 and 12.2 % only respectively [8].

One study in Pakistan in 2004, showed gram negative isolates as 56.63 % and gram positive as 43.37 % [13]. The Indian data showed predominantly higher frequency of infections with gram negative micro-organisms 75.8 % (*Klebsiella pneumoniae* the most frequent) while gram positive micro-organisms was 24 % [14]. Study from Turkey reported gram negative micro-organisms as 58.4 % and gram positive as 36.1 % among the documented cultures in febrile neutropenia [15].

Coagulase negative *S. aureus* (CoNS) had been the commonest micro-organism isolated in western countries while *E. coli*, *P. aeruginosa* and *Klebsiella* species had been the frequently gram negative isolated pathogens [7, 11]. This data showed enterobacteriaceae group comprised of nearly 50 % and among gram negative organisms and *E. coli* was the predominant (28.8 %).

The gram positive isolates constituted frequency of 45 % in this data which is although slightly less than the gram negative isolates (49 %) but still poses an alarmingly increasing trend. They were previously said to be less common in developing countries by various studies especially Pizzo et al. [4]. These figures are showing a progressively rising frequency in another regional study as well [13]. Methicillin sensitive *Staph Aureus* is found to be the commonest gram positive micro-organism in this study in 21 cases among them six were MRSA, which is again showing rising trend. The results from published data from same institution in 2006 exhibited only seven gram positive isolates among 120 blood cultures and had only single case of MRSA. Large number of MRSA isolates from patients is a dilemma as delay in starting their treatment can raise the mortality rate of the institute. In comparison to these results only single case of MRSA was found among gram positive isolates from Indian study while three cases were isolated from Turkish study [14, 15].

There is also increasing frequency of isolation of documented fungal infections and we are able to document three cases of radiologically proven invasive fungal infection. They were treated with systemic Amphotericin and among them two were rescued. The Turkish data showed six documented fungal isolates among them 5 were *Candida* species.

Among gram positive organisms, only 66 % of isolates were sensitive to Vancomycin and 50 % were sensitive to Amikacin, while Teicoplanin exhibited 75–100 % sensitivity. Coagulase negative Staph was grossly (80 %) sensitive to Ceftazidime and Amikacin (the first-line antibiotics for treatment of febrile neutropenia at that time) along with same 80 % sensitivity to Vancomycin and Ciprofloxacin. The Enterococci showed 75 % sensitivity to Vancomycin and third generation cephalosporin; however

one case of Vancomycin Resistant Enterococci was isolated. *Streptococcus viridians* which was isolated in four cases (8 %).

Among gram negative organisms the most frequent isolate was *E. coli*, 33 % sensitive to the Ceftazidime and 86 % sensitive to Amikacin. Meanwhile our first-line antibiotics weren't able to cover more than 50 % of frequently found organisms (both gram negative and gram positive organisms) in this data. Pipracilin/Tazobactam was showing more than 80 % cover for all three frequent gram negative bacilli along with Staphylococci. Carbapenem group was still showing more than 90 % sensitivity. Considering this data the antibiotic policy was changed for febrile neutropenia in patients with hematological malignancies.

Conclusion

Febrile neutropenia is a hematological emergency always requires effective and broad spectrum coverage for the offending organisms so ever there is a need for serial surveillance of our clinical data. Although gram negative infections still predominate but there is an alarming rise in resurgence of gram positive micro-organisms. Our first-line antibiotics were not able to cover most of the frequently encountered organisms which compelled us to change our treatment choice.

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