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Incidence of Drug Resistance among Bacteria Isolated from Neutropenic Cancer Patients undergoing Chemotherapy

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Infection remains major complication and cause of morbidity in neutropenic cancer patients. A total of 211 clinical samples were collected from 102 patients suffering from different types of malignancies and developed neutropenia. Over all 67(31.75%) samples were positive for bacterial growth. Of there 19 positive were from blood, 32 that of urine, 09 of pus, 05 sputum, one each from stool and throat swab. A total of 70 bacterial isolates belonged to seven different species were obtained from these samples. Out of these 52.86% were gram negative bacilli and 47.14% were gram positive cocci. *E.coli* was the predominant organism among patients and accounted for 19 (27.14%) in all samples. In the blood highest infective organism was coagulase negative *Staphylococcus* and accounted for 08(42.10%). High degree of resistance observed in gram negative pathogens. *E.coli* 19(100%) showed resistance against cefaclor, cefuroxime and amoxicillin plus clavulanate. Eight strains of *Klebsiella pneumoniae* showed resistance against ceftazidime 8 (73%), cefixime 7 (64%) and to ofloxacin 8(73%). Three strains (21%) of *Staphylococcus aureus* showed resistant to methicillin. *Streptococcus pyogenes* showed sensitivity to imipenem and erythromycin. Half of *Enterococcus faecalis* were resistant to vancomycin. Continuous monitoring of bacterial shift and use of appropriate antibiotic agents reduced morbidity and prolonged survival of neutropenic cancer patients.

Key Words: Neutropenia, Infection, Cancer, Chemotherapy.

Cancer is a fatal and leading cause of death worldwide. Chemotherapy regimes depress the normal function of bone marrow resulting in the decrease of number of white blood cells, red blood cell and platelets and the patient becomes immunocompromised and susceptible to infection.[1] Neutropenia is a most common adverse effect of chemotherapy. The Severity of infection depends on duration of neutropenia, if neutropenia remains at least for five weeks the frequency of infection is 100% [2]. Infection remains a major complication and the cause of morbidity in cancer patients and bacteremia is one of the most common serious complications in febrile neutropenia cancer patients.[3] Use of empirical antimicrobial therapy in neutropenic cancer patients is subject to controversy as over the past decades. The major changes have been witnessed in pathogens with respect to epidemiology and drug resistance at national and international level.[4] The changing pattern of pathogens, rapid development of bacterial resistant and emergence of new clinical problems imposed extra burden on clinicians to manage neutropenic cancer patients. It is therefore

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imperative that microbiological profile for antibiotic sensitivity pattern is known before empirical or therapeutic use of antibiotics. The aim of this study to assess the prevalence of different bacterial agents and estimate antimicrobial resistance in neutropenic patients

MATERIALS AND METHODS

The study was conducted in the department of Microbiology at Mohan Dai Oswal Cancer Hospital, Ludhiana (India) over a period of two years from May, 2008 to May, 2010. A total of 102 patients suffering from various types of malignancies and undergoing chemotherapy leading to neutropenia were taken as subjects of this study. Patients suffering from hematological malignancies and developing systemic solid tumors were including in this study. Fever was determined by oral temperature > 38.3^{0}C or for more than one hour in febrile patients.[5] Haemogram was done in all patients to diagnose neutropenia. All clinical samples were collected from patients during their stay in hospital. Collected samples comprised of blood, urine, pus, throat swabs, sputum, stool and aspirated body fluids.

All clinical specimens were collected using standard procedures in aseptic pre-sterilized containers to avoid contamination and sent to microbiology laboratory without delay. Blood samples were obtained aseptically from peripheral veins of the patients when they develop fever before antibiotic initiation. Five ml of blood was withdrawn from peripheral vein of the patient and directly inoculated in blood culture bottles containing 50 ml brain heart infusion broth and incubated at 37°C for at least 1 week and inspected after every two days interval to determine turbidity. Positive blood cultures were determined if culture bottles showed turbidity. The subculture was made

Table 1. Total Number of Samples examined from different patients

S.No.	Specimen	No. of Sample	Cultures growth	No growth	Infectivity Per cent
1.	Blood	90	19	71	21.11
2.	Urine	82	32	50	39.02
3.	Pus	16	09	07	56.25
4.	Sputum	07	05	02	71.42
5.	Aspirated Fluids	07	00	07	00.00
6.	Stool	06	01	05	16.16
7.	Throat Swab	03	01	02	33.33
Total	07	211	67	144	31.75

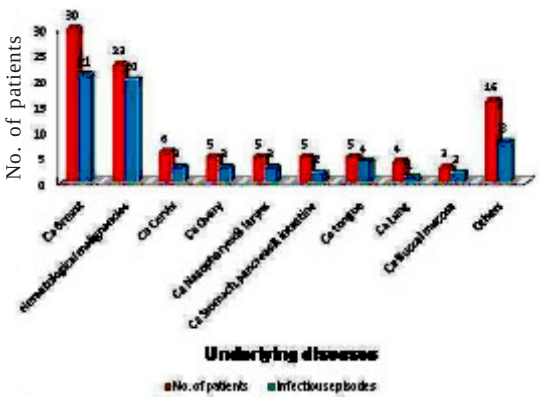

Fig. 1. Incidence of infectious episodes and underlying diseases.

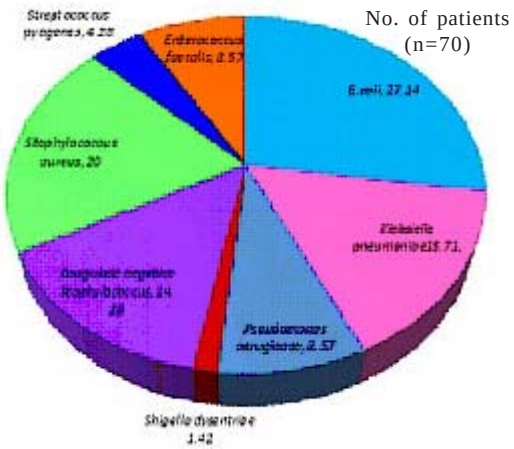

Fig. 2. Frequency and percentage of pathogenic organisms isolated from neutropenic cancer patients

on blood agar and MacConkey agar plate from positive culture bottles and incubated aerobically again for 24 hours, growth was determined by visual observation. Other clinical samples such as urine, pus, throat swabs, stool, and aspirated body fluids were taken for bacteriological examination at different intervals during the course of disease. Morphological characteristics, shapes and arrangements of bacterial cells were studied by Gram's staining. The antimicrobial sensitivity test was carried out by disc diffusion method. The results were interpreted as per guidelines of national committee for clinical laboratory standard.[6]

Data analysis

For statistical analysis, the chi-square test was applied. The data was compiled by using SPSS software for Windows version 12 and p values were worked out by applying Z- test. A p-value of<0.05 was considered to be statistically significant.

RESULTS

One hundred and two patients who visited the hospital for undergoing chemotherapy were included in this study. Among these there were 44 males and 58 females. A total of 211 samples were collected from among patients. (Table 1) The underlying diseases and infectious episodes among patients depicted in figure 1. All samples showed statistically highly significant results ($p<0.002$) except throat swabs. However, the aspirated are samples also showed significant results but statistically it is considered as failure because none of samples showed microbial growth. A total of 70 bacterial isolates belonged to seven different species were identified (figure 2).Out of these 52.86% were gram negative bacilli and 47.14% were gram positive cocci but statistically there was no difference ($p>0.05$) in epidemiological ratio of gram positive and gram negative bacteria. The distribution of pathogenic bacteria in different clinical samples shown in table 2.Urine is the major source of infection and highest infective organism isolated was *E.coli* 12(37.5%) followed by *Staphylococcus aureus* 06(18.75%), *Enterococcus faecalis* 05(15.62%), *Klebsiella pneumoniae* 04 (12.50%), and *Pseudomonas aeruginosa* and coagulase negative *Staphylococcus* each 02(6.25%), *Streptococcus pyogenes* 01(3.42%). Significant isolation ($p<0.004$) of bacteria was obtained from urine samples. In the blood highest infective organism was coagulase negative Staphylococcus and accounted for 08(42.10%)

Table 2. Distribution of pathogenic bacteria in different clinical samples

S. No.	Pathogen	Clinical specimens						
		Urine	Blood	Pus	Stool	Sputum	Throat swab	Aspirated fluids
1.	*E.coli*	12 (37.5%)	02 (10.53%)	02 (20%)	00 (00%)	03 (42.85%)	00 (00%)	00 (00%)
2.	*Klebsiella pneumoniae*	04 (12.5%)	03 (15.79%)	02 (20%)	00 (00%)	01 (14.29%)	01 (100%)	00 (00%)
3.	*Pseudomonas aeruginosa*	02 (6.25%)	00 (00%)	02 (20%)	00 (00%)	02 (28.57%)	00 (00%)	00 (00%)
4.	*Staphylococcus aureus*	06 (18.75%)	03 (15.79%)	04 (40%)	00 (00%)	01 (14.29%)	00 (00%)	00 (00%)
5.	Coagulase negative *Staphylococcus*	02 (6.25%)	08 (42.10)	00 (00%)	00 (00%)	00 (00%)	00 (00%)	00 (00%)
6.	*Streptococcus pyogenes*	01 (3.13%)	02 (10.52%)	00 (00%)	00 (00%)	00 (00%)	00 (00%)	00 (00%)
7.	*Enterococcus faecalis*	05 (15.62%)	01 (5.26%)	00 (00%)	00 (00%)	00 (00%)	00 (00%)	00 (00%)
8.	*Shigella dysenteriae*	00 (00%)	00 (00%)	00 (00%)	01 (100%)	00 (00%)	00 (00%)	00 (00%)

followed by *Staphylococcus aureus* and *Klebsiella pneumoniae* each 03(15.78%), *E.coli* and *Streptococcus pyogenes* 02(10.53%) and *Enterococcus faecalis* 01(5.26%). Significant infectivity ($p<0.009$) was observed in blood samples.

In pus samples *Staphylococcus aureus* was frequently isolated 04(40%) followed by 2(20%) each *E.coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The sputum specimen showed the presence of *E.coli* 03 (42.85%) followed by *Pseudomonas aeruginosa* 02(28.57%) and *Staphylococcus aureus* and *Klebsiella pneumoniae* each 01(14.29%). *Shigella dysenteriae* was the only organism isolated from stool sample. *E. coli* was observed in majority in urine samples and coagulase negative *Staphylococcus* was frequently isolated from blood samples. Pus, sputum, stool and throat swabs showed less rate ($p>0.05$) of infectivity. Overall analysis showed that most of the bacteria were isolated from urine and blood samples.

Bacterial infections may be preventable by prophylactic antibiotic agents. Resistance to antibiotics poses a threat to everyone, but neutropenic cancer patients are particularly at risk. A total of seventy isolates were selected for sensitivity test. We used single antibiotic agents as well as combinations of two different groups of antibiotics. Eleven isolates of *E.coli* (58%) and 08 *Klebsiella pneumoniae* (73%) resistant to ceftazidime. All gram negative isolates except *Klebsiella pneumoniae* were sensitive to piperacillin plus tazobactam and imipenem. Among

Table 3. Antimicrobial resistance (%) patterns in Gram-negative bacteria

Organism	Interpretation	AK	GM	KF	FG	CF	RP	SF	AG	ZN	GF	CB	MG	TZP	IM
	S	15	08	00	05	02	03	16	00	4	19	00	15	19	19
E.coli		(79)	(42)	(00)	(26)	(11)	(16)	(84)	(00)	(21)	(100)	(00)	(79)	(100)	(100)
(n=19)	I	00	03	00	03	00	00	00	00	02	00	00	00	00	00
		(00)	(16)	(00)	(16)	(00)	(00)	(00)	(00)	(11)	(00)	(00)	(00)	(00)	(00)
	R	(04)	08	19	11	17	(16)	03	19	13	00	19	04	00	00
		21	(42)	(100)	(58)	(89)	84	(16)	(100)	(68)	(00)	(100)	(21)	(00)	(00)
	S	05	07	00	02	00	01	02	00	02	09	02	09	10	09
Klebsiella pneumoniae		(45)	(64)	(00)	(18)	(00)	(10)	(18)	(00)	(18)	(82)	(18)	(82)	(91)	(82)
(n=11)	I	01	00	00	01	00	00	02	00	01	00	00	00	00	00
		(09)	(00)	(000	(09)	(00)	(00)	(18)	(00)	(09)	(00)	(00)	(00)	(00)	(00)
	R	05	04	11	08	11	10	07	11	08	02	08	02	01	02
		(46)	(36)	(100)	(73)	(100)	(90)	(64)	(100)	(73)	(18)	(82)	(18)	(09)	(18)
	S	04	01	00	04	02	04	01	00	02	03	00	06	06	06
Pseudomonas aeruginosa		(67)	(17)	(00)	(67)	(33)	(67)	(17)	(00)	(33)	(50)	(00)	(100)	(100)	(100)
	I	00	01	00	00	00	00	01	00	00	00	00	00	00	00
		(00)	(17)	(00)	(00)	(00)	(00)	(17)	(00)	(00)	(00)	(00)	(00)	(00)	(00)
	R	(2)	04	06	02	04	02	04	06	04	03	06	00	00	00
		33	(67)	(100)	(33)	(67)	(33)	(67)	(100)	(67)	(50)	(100)	(00)	(00)	(00)
	S	01	01	00	01	01	00	00	00	00	01	00	01	01	01
Shigella dysenteriae		(100)	(100)	(00)	(100)	(100)	(00)	(00)	(00)	(00)	(100)	(00)	(100)	(100)	(100)
(n=1)	I	00	00	00	00	00	00	00	00	00	00	00	00	00	00
		(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)
	R	00	00	01	00	00	01	01	01	01	00	01	00	00	00
		(00)	(00)	(100)	(00)	(00)	(100)	(100)	(100)	(100)	(00)	(100)	(00)	(00)	(00)

AK=Amikacin, GM=Gentamicin, KF= Cefaclor, FG= Ceftazidime , CF=Cefotaxime , RP= Cefatrizone, SF= Cefixime, AG=Amoxcillin+clavulanate,ZN=Ofloxacin, GF=Gatifloxacin, B=Cefuroxime, MG=Cefoperaxone+salbactam, TZP=Piperacillin+Tazobactam, IM=Imipenem

Table. 4 Antimicrobial resistance (%) patterns in Gram-positive bacteria

Organism	Interpre-tation	AK	AG	GM	MR	ZN	GF	MG	LX	CX	ER	VA	IM
Staphylococcus aureus(n=14)	S	14(100)	03(22)	07(50)	11(79)	02(14)	12(86)	10(71)	07(50)	07(50)	05(36)	06(43)	13(93)
	I	00(00)	02(14)	01(07)	00(00)	01(07)	00(00)	00(00)	00(000	00(000	01(07)	00(0)	01(07)
	R	00(00)	09(64)	06(43)	03(21)	11(79)	02(14)	04(29)	07(50)	07(50)	08(57)	08(57)	01(070
Coagulase negative Staphylococcus (n=10)	S	10(100)	05(50)	10(100)	06(60)	05(50)	08(80)	10(100)	04(40)	08(80)	06(60)	09(90)	10(100)
	I	00(00)	02(20)	00(00)	00(00)	01(10)	00(00)	00(00)	02(20)	01(10)	02(20)	00(00)	00(00)
	R	00(00)	03(30)	00(00)	04(40)	04(40)	02(20)	00(00)	04(40)	01(10)	02(20)	01(10)	00(00)
Streptococcus pyogenes(n=3)	S	03(100)	03(100)	01(33)	—-	01(33)	03(100)	01(33)	02(67)	01(33)	01(33)	02(67)	03(100)
	I	00(00)	00(00)	00(00)	—-	00(00)	00(00)	00(00)	00(00)	00(00)	00(00)	00(00)	00(00)
	R	00(00)	00(00)	02(67)	—-	02(67)	00(00)	02(67)	01(33)	02(67)	02(67)	01(33)	00(00)
Enterococcus faecalis(n=6)	S	03(50)	03(50)	02(33)	—-	05(83)	02(33)	04(67)	03(50)	02(33)	02(33)	03(50)	04(67)
	I	00(00)	00(00)	00(00)	—-	00(00)	00(00)	00(00)	00(00)	00(00)	00(00)	00(00)	00(00)
	R	03(50)	03(50)	04(67)	—-	01(17)	04(67)	02(33)	03(50)	04(67)	04(67)	03(50)	02(33)

AK=Amikacin, Amoxcillin+clavulanate, GM=Gentamicin ,MR=Methicillin, ZN=Ofloxacin,GF= Gatifloxacin, MG= Cefoperxone+salbactam, LX=Lincomycin, CX=Cloxacillin ER=Erythromycin, VA= Vancomycin, ,IM=Imipenem. S= Sensitive, I= Intermediate resistant, R= Resistant

gram positive bacteria 09(64%) *Staphylococcus aureus* showed resistance against amoxicillin plus clavulanate while half of coagulase negative Staphylococcus resistant to amoxicillin plus clavulanate and ofloxacin. All gram positive isolates except *Enterococcus faecalis* were sensitive to amikacin. Overall results of resistance are shown in Table no. 3 and 4.

DISCUSSION

Bacterial infections are the major cause of mortality and morbidity in neutropenic cancer patients undergoing chemotherapy.[5,7] Bacterial infections in such patients are differ from institute to institute and influenced by factors such as use of prophylactic antimicrobial agents. The treatment of neutropenic patients is possible by adoption of successful empirical antimicrobial therapy to eliminate the majority of bacterial pathogens. In 1970s gram negative organisms were predominant (70%) in bloodstream infection and morbidity caused by these organisms reported as forty per cent[8]. Epidemiological shift in types of bacteria have occurred internationally from gram negative to gram positive bacteria in mid of 1980s in most hospitals.[9-10] Although the reason behind this statement is not clear but the causes of these changing trends in pathogens are the administration of aggressive chemotherapy, radiation regimes that cause severe mucosititis, prolonged use of in dwelling catheters and wide spread use of prophylactic agents such as flouroquinalones and empirical treatment against gram negative bacteria[7].In the present study overall gram negative pathogens were more predominant and accounted for 52.86% and 47.14% were gram positive pathogens. Mahmud *et al* observed the ratio of gram positive and negative bacteria as 57.7% and 42.3% respectively in a study in Pakistan. *Staphylococcus aureus* was common isolate among gram positive bacteria whereas *E.coli* was predominant organism amongst gram negative bacteria followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.[11] A definite shift towards gram positive bacteria was observed in our study. We found that gram positive pathogens were predominant in bloodstream infection. Results indicated that 73.68% were gram positive pathogens and 26.32% were gram negative in bloodstream infection. Our results are in agreement with Lyytikainen *et al* , they reported 65% of bloodstream infection caused by gram positive bacteria in same setting [12] Bacteremia caused by gram positive bacteria reported 62% in study conducted by Berjan *et al* . Coagulase negative *Staphylococcus* accounted for 42.5% among gram positive pathogens.[13] Our study agrees with Bergian *et al*, among gram positive bacteria coagulase negative *Staphylococcus* was most common (42.10%) isolate in blood samples in present study. The ratio of gram positive and gram negative bacteria is a subject of changing. Very recently change in the etiology pattern of pathogens has been observed. A classical study by Haupt *et al* revealed an increase of 3.4% per year in the incidence of gram negative bacteremia in children treated for cancer in Italians institute [14].

The rate of isolation of causative pathogens from clinical samples varied from 22% to 39% of cases.[9,16] We described 21% infectivity rate in blood samples of neutropenic cancer patients. A total of 19 bacterial pathogens were identified and coagulase negative *Staphylococcus* (42.10%) was predominant pathogen followed by *Klebsiella pneumoniae* and *Staphylococcus aureus* (15.79%). Another study showed mortality rates associated with infection caused by coagulase negative Staphylococci (33.4%) and other gram positive organisms encountered were methicillin-susceptible *Staphylococcus aureus* and methicillin- resistance *Staphylococcus aureus* 22.8% and 17.7% respectively.[15] Hospital acquired infection was most common infection and responsible for 77% cases of bacteremia.[16] Jardin *et al* pointed out that bacteremia among patients due to hospital etiology.[17]

The overall spectrum of infection in cancer patients may be different from associated with bloodstream infection. The present study not only observed the bloodstream infection but also urinary tract infections, respiratory tract infections, gastrointestinal infections, wounds and pyogenic infections to get a complete spectrum of pathogenic bacteria in cancer patients. *E.coli* was the most common isolate causing urinary tract infection and coagulase negative *Staphylococcus* was found to be second most common pathogen.[18] In contrast to other researcher urine sample obtained from hospitalized patients are likely to be infected with

Enterococcus, which has emerged as the second most common cause of hospital acquired infection.[19] Urinary tract infection caused by *Pseudomonas aeruginosa* was associated with nosocomial infection due to long term use of catheterization.[20] Wolday and Erge isolated *Pseudomonas aeruginosa* from urine samples of patients undergoing surgery.[21] These two studies concluded that bacteria was of nosocomial origin. The upper respiratory tract infection is most common in cancer patients and cause of motality.[22] Sputum samples showed high infectivity rate, 05 out of 07 were positive for bacterial growth in our study. Gram negative including *E.coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were commonly isolated from neutropenic cancer patients, whereas patients who have B-cell defect are more prone to gram positive bacteria such as *Streptococcus pneumoniae* and *Staphylococcus aureus*.[23] Surgical site infections are common in cancer patients undergoing surgical procedures. We observed that surgical infections have high incidence of bacterial infection. *Staphylococcus aureus* was the most common isolate. In contrast to other researcher surgical infections caused by gram negative bacteria.[24] Similar results were reported by Gedebou *et al* and Habte *et al*.[25-26] The rate of surgical site infections is comparatively less in other studies [27]. Barber *et al* pointed out that surgical site infections in cancer patients were variable ranged from 39 to 48.9 per cent. The authors speculated that variability depends on duration of surgical procedure [20].

The development of resistance to antibiotics in hospitalized neutropenic cancer patients is well recognized. Our study indicated highly documented increasing rates of drug resistance in majority of pathogens. A change in antimicrobial resistant pattern of bacteria in neutropenic cancer patients has occurred in past few years. The résistance is markedly increased in common antimicrobial agents in our study and as compared with other studies.[19-28] Significant antimicrobial resistance was observed in gram positive bacteria in our study. Karim *et al* reported that fifty per cent of *Staphylococcus aureus* showed resistance to cloxacillin and 57% against erythromycin in a study conducted in pakistan.[29] Vancomycin is only used for treatment when infection is caused by gram positive organism, because of raising resistance. Vancomycin only used when there is evidence of soft tissue and septic infections. Vancomycin may add with short duration of fever and quick defervenscence in patients with gram positive infections.[30] Our study indicated that 50% *Enterococcus faecalis* were resistant to vancomycin. A similar resistance has been recognized in a study in Pakistan[31]. Many studies suggested that newer generation of quinolones such as gatifloaxacin and moxifloxacin were more effective than ciprofloxacin and ofloxacin in prophylaxis of cancer patients [32-33]. A study on similar antibiotics was carried out in Egypt. The results showed 33.3% *Staphylococcus aureus* were resistance to gatifloaxacin, and 60.9% to ofloxacin. In coagulase negative *Staphylococcus* this pattern indicated 27.3% and 53.1% resistant to these antibiotics[34]. In our study 14% *Staphylococcus aureus* and 20% coagulase negative *Staphylococcus* were resistance to gatifloaxacin whereas ofloxacin showed 79% resistance in *Staphylococcus aureus* and 40% in coagulase negative *Staphylococcus*. On the other hand some studies suggested that high dose of old quinolones such as ciprofloxacin were more effective as monotherapy for treatment of neutropenic cancer patients[35] while some studies recommended advanced quinolones like clinafloxacin.[36] Markedly increased antimicrobial resistance to routine antibiotics in gram negative isolates has occurred in our study. Tariq *et al* reported 27*% E.coli* were resistant to cefixime[37]. Suzan *et al* reported 89% strains of *E.coli* were resistant to amikacin.[3]

There are many empirical regimes suggested for the treatment of neutropenic cancer patients. A combination of anti pseudomonal carboxypenicillin or piperacillin plus tazobactam has been recommended as standard initial therapy for these patients. The resistance to piperacillin plus tazobactam was reported very less in gram negative bacteria in cancer patients.[37] Our study indicated 100% sensitivity to above said combination in all gram negative pathogens except only a signal strain of *Klebsiella pneumoniae* which was found to be resistant to this combination. Aminoglycosides combination with third generation of cephalosporin (cefoperazone and ceftazidime) has been used and over all response ranging 71 to 76% in neutropenic patients[38-39]. Cefepime and imipenem have

previously been used as empirical therapy for cancer patients with fever and neutropenia[39-41]. The efficacy of these drugs has explained in various studies[42-44]. Advent of broad spectrum antibiotics cephalosporin and carbapenem are used as single regimen. Many studies reported that single drug therapy is safe, effective as aminoglycosides containing regimes. Imipenem was found to be equally effective compared to ceftazidime plus amikacin and imipenem plus amikacin. This study determined that if imipenem is administered as monotherapy it will be superior to ceftazidime.[39] The infectious disease society of America has recommended ceftazidime as a first line of antimicrobial agent as empirical treatment in febrile neutropenic patients.[15] In our study, we found that majority of gram negative bacteria developed resistance against ceftazidime. Significant sensitivity was observed in majority of pathogens against carbapenem antibiotic such as imipenem in our study and it is highly recommended antimicrobial agent.

CONCLUSION

Neutropenic patients in our study appear to be changing with shift towards gram positive organisms causing bloodstream infections and majority of pathogens were resistant to various antimicrobial agents. The monitoring of bacterial shift must be observed to reduce mortality in neutropenic patients. Appropriate guidelines should be adopted for the use of prophylactic and therapeutic antibiotics which would improve the outcome and prolonged survival in cancer patients with neutropenia.

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