

## ORIGINAL ARTICLE

# Blood stream infection among the febrile neutropenic patients suffering from hematological disorders at a tertiary care centre, North India

Munesh Kumar Gupta<sup>1</sup>, Ravikant Sharma<sup>2</sup>, Nilesh Kumar<sup>3</sup>, Ranjan Bhattanagar<sup>4</sup>, Pankaj Kannauje<sup>4</sup>, Vijay Parashar<sup>5</sup>, Kailash Kumar<sup>6</sup>

**Authors'Affiliation:** <sup>1</sup>Asst. Prof., Dept of Microbiology, IMS BHU, <sup>2</sup>Junior resident; <sup>3</sup>Asso. Prof; <sup>4</sup>Asst Prof., Dept. of General Medicine, IMS BHU, <sup>5</sup>Senior Resident, Institute of Dental Sciences, <sup>6</sup>Prof., Dept. of General Medicine, IMS BHU

**Correspondence:** Dr. Nilesh Kumar, Email: nilesh19arreno@gmail.com

## ABSTRACT

**Introduction:** Blood stream infections are the common infectious consequence in neutropenic patients suffering from the hematological malignancies. These infections are usually caused by a diverse group of microbes.

**Material and methods:** A pair of blood culture was executed in the febrile neutropenic patients suffering from hematological disorders, to observe the microbiology of the blood stream infections. Identification and antimicrobial susceptibility testing were performed as per standard microbiological procedures.

**Results:** In the present study, 27% of blood culture positivity (27/100) was observed among the enrolled febrile neutropenic patients. Gram-positive cocci including *Staphylococcus aureus* (n=15), Coagulase negative staphylococci (n=8), *Enterococcus faecalis* (n1) were the predominance in comparison to Gram negative microbes (one each isolate of *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*). All the isolated Gram-positive microbes were sensitive to vancomycin and linezolid. 65.2% of isolated *Staphylococci* were methicillin resistant (15/23). One MDR *Klebsiella pneumoniae* strain was also isolated, having a susceptibility to only carbapenem and polymyxin B.

**Conclusion:** Blood culture and susceptibility testing should be performed in each case of febrile neutropenia as blood stream infections among these patients are caused by a divergent group of microbes having a varied susceptibility pattern.

**Key words:** Blood stream infection, febrile neutropenia, hematological disorders

## INTRODUCTION

Neutropenia is a frequent complication in the patients, suffering from the hematological disorders which is characterized by the less than or equal to 500 cells per mm<sup>3</sup> or expected to fall in next 48hrs.<sup>1</sup> Neutrophils are an important defense mechanism against the outsider microbes. In such neutropenic patients, both blood stream and respiratory infections are quite common.<sup>2</sup> Prompt diagnosis and treatment of these infections, among the neutropenic patients, is a need as untreated or delayed treatment is associated with higher morbidity and mortality. Fever is a common event in such patients which is not only due to the invading microbes but also may be a consequence of the chemotherapy or disease itself. Febrile neutropenia is defined as an oral temperature of >38.3°C or two consecutive readings of

>38.0°C for 2 hr with low (<500/mm<sup>3</sup>) absolute neutrophil counts.<sup>3</sup>

Blood stream infections (BSI) among these patients are usually caused by the drug resistant microbes. Globally, Gram-positive cocci have been reported the most common cause of BSI, among these neutropenic patients, with a declined prevalence of Gram negative microbes.<sup>4</sup> *Staphylococci* are the worldwide, predominant isolated microbes in these patients which show a variable drug-resistance especially against the  $\beta$ -Lactam group of antibiotics by a production of penicillinase enzyme and by an alteration in the penicillin-binding protein 2a (PBP2a).<sup>6</sup> Against this background, a study was conducted to determine the microbiology of BSI with their antibiogram, in the febrile neutropenia patients suffering from the hematological disorder.

**MATERIAL AND METHODS**

The present prospective study was conducted among the febrile neutropenic patients suffering from hematological disorders from duration of Nov 2016 to May 2018. A well written informed consent was taken from all participants. A pair of biphasic culture media containing both solid and liquid phase was used to execute the blood culture. For each biphasic media, 5ml of the blood from the two different sites was collected and transferred immediately to the liquid phase of biphasic media. These biphasic media were incubated at 37°C on ambient air. Once the growth was observed on solid phase of biphasic media, growth was processed further by standard microbiological procedures including Gram’s stain; biochemical testing for the identification.<sup>7</sup> Antimicrobial susceptibility testing against the isolated bacteria was performed by the Modified Kirby Bauer methods. For Gram-positive bacteria, following disc, 10Units of the penicillin, 15mcg of erythromycin, 125mcg+ 23.75mcg of trimethoprim+ sulphamethoxazole, 30mcg of linezolid, 30mcg of netilmicin, 5mcg of moxifloxacin and 10mcg of gentamycin were used. 30mcg of cefoxitin was used to determine the methicillin-resistant property of the staphylococci.<sup>8</sup> To determine the vancomycin susceptible Staphylococci, vancomycin screen agar containing 6mcg/ml vancomycin was used.<sup>9</sup> For Gram negative bacteria, following disc 10mcg of the ampicillin, 20 mcg +10 mcg of amoxicilin+ clavulanic acid, 10mcg of Gentamicin, 5mcg of ciprofloxacin, 25mcg+ 23.75 mcg of trimethoprim+ sulphamethoxazole, 5mcg of levofloxacin, 30mcg of cefotaxime, 30mcg of amikacin, 30mcg of cefepime, 100mcg+10mcg of piperacillin +tazobactam, 10mcg of imipenem, 10mcg of meropenem and 200mcg of polymyxin B was used.

For non-fermenters, especially Pseudomonas aeruginosa, 100mcg of piperacillin and 30mcg of ceftazidime disc were added further. Results were interpreted according to the CLSI guidelines.<sup>9</sup>

**RESULTS**

A total of 100 cases of febrile neutropenia were enrolled in the present study among whom the microbiology of the BSI was determined. Febrile neutropenia was observed in 41% aplastic anemic patients followed by myelodysplastic syndrome (17%) and acute leukemia (9%). A total of 27 microbes were isolated from the febrile neutropenic patients among whom 24 were Gram-positive, rest being the Gram negative microbes. Among the Gram-positive cocci, Staphylococcus aureus (n=15) were outnumbered in comparison to Coagulase negative Staphylococci (n=8) and Enterococcus faecalis (n=1). Single strain of each Klebsiella pneumoniae, Escherichia coli, and Pseudomonas aeruginosa were also isolated. (Table 1)

Among the isolated strains, nine S.aureus and six Coagulase negative staphylococci strains were methicillin resistance, which was determined by using the 30mcg cefoxitin disc. Among the 23 isolated strains of the Staphylococci, 15 were methicillin resistant. A 100% susceptibility of the netilmicin, vancomycin (by vancomycin screen agar) and linezolid was observed against the isolated staphylococci (n=23) strains.(Table2 Three gram negative bacteria were also isolated from the patients suffering from the febrile neutropenia. One isolated Klebsiella pneumoniae strain was only sensitive to carbapenem group of drug and polymyxin B.

**Table 1: Antibacterial susceptibility testing of the Gram-negative bacteria isolated from the blood culture**

	Am	Pip	Amc	Ceft	Gn	Cip	Lv	Cft	Amk	Cp	Ptz	Im	Me	PolB
K.pneumoniae	R	R	R	R	R	R	R	R	R	R	R	S	S	S
E.coli	R	R	R	R	S	R	R	R	S	R	R	S	S	S
P.aeruginosa	NA	S	NA	S	S	S	S	S	S	S	S	S	S	S

1. Antibiotics disc: Am:ampicillin, Pip: Piperacillin, Amc: Amoxicillin-clavulanic acid, Ceft:Ceftazidime, Gn:Gentamycin, Cip: Ciprofloxacin, Lv: Levofloxacin, Cft: Cefotaxime, Amk: Amikacin, Cp: Cefepime, Ptz: Piperacillin-tazobactam, im: Imipenem, Me:Meropenem, PolB: Polymyxin B
2. S: sensitive, R: Resistant, NA: not applied

**Table 2: Number of isolated staphylococcal strains having sensitive antibacterial pattern**

Organism	Ery	Cotri	Vanc	Linezolid	Moxifloxacin	Netilmicin	Gentamycin	Ciprofloxacin
MRSA (n=9)	1	3	9	9	6	9	9	4
MSSA (n=6)	6	2	9	9	5	9	5	0
MRCoNS (n=6)	0	1	9	9	4	9	3	3
MSCoNS	2	2	9	9	2	9	2	1

Ery=Erythromycin, Cotri=Cotrimoxazole, Vanc=Vancomycin

## DISCUSSION

Blood-stream infection is a significant cause of morbidity and mortality among the neutropenic patients, suffering from hematological disorders.<sup>10</sup> These patients are highly vulnerable to respiratory and disseminated infections which are caused by diverse groups of microbes. Both bacterial and fungal pathogens are associated with blood stream infection among such type of patients.<sup>11</sup> Prompt diagnosis with appropriate treatment of these microbes reduces the morbidity and mortality.<sup>10</sup> Blood culture is routinely executed to determine the causative agent of the blood stream infection but the sensitivity of these blood cultures is poor with a range of 15-25%.<sup>10,12,13,14</sup> The molecular method has a higher detection rate (43%) among these patients.<sup>14</sup> In the present study, we only got the culture positivity rate of 27%. Poor sensitivity of the blood culture may be attributed to the previous antibiotics uptake as at our tertiary care center, most of the cases are referred from the periphery.<sup>15</sup> Fever in neutropenic patients suffering from the hematological disorders may be non-infectious in origin as high temperature have been reported in the hematological malignancies and other inflammatory disorders.

In the present study, Staphylococci (n=23) were the most frequent isolates from the Blood. Only three gram negative microbes were isolated. A similar type of the results, Staphylococci the most predominant isolates, have been reported by Ibrahim et al.<sup>5</sup> Among these isolates Staphylococci strains (n=23), 15 strains were methicillin resistant, which means they are resistant to all  $\beta$ -Lactam group of antibiotics including a combination with  $\beta$ -Lactamase inhibitors.<sup>8</sup> In these cases, other groups of antibiotics as glycopeptides, macrolides, fluoroquinolones and aminoglycoside are widely used in the treatment. In our present study, a varying sensitivity to the macrolides, fluoroquinolone, and aminoglycoside was observed against the isolated Staphylococci. Care should be taken regarding the use of aminoglycoside in combination with cell wall acting agents as  $\beta$ -Lactam and glycopeptide group of drugs.<sup>9</sup> In such cases, the glycopeptide group of antibiotics, vancomycin, and linezolid can be used.<sup>17</sup> Penicillinase-resistant  $\beta$ -Lactam group of antibiotics are superior in the treatment of methicillin-sensitive strains of the Staphylococci.<sup>18</sup>

In our study, the gram-negative bacteria were associated in only 3% of the BSI. Isolated one strain of the *Klebsiella pneumoniae* was resistant to  $\beta$ -Lactam, cephalosporins, fluoroquinolone, sulfa drugs, aminoglycoside, being the sensitive to only carbapenem & polymyxin group of drugs whereas another *Escherichia coli* isolate was sensitive to only aminoglycoside and carbapenem. In such scenario, appropriate

diagnosis and antibiogram of the causative agent of the BSI is a need for patient survival.

Most of the isolated strains whether Gram positive or Gram negative were resistant to common  $\beta$ -Lactam groups of antibiotics. These strains were also resistant to other different groups of antibiotics. In such cases, use of  $\beta$ -Lactam group of antibiotics as a presumptive treatment is highly questionable. In the present study, the Staphylococci were the most common causative agent having a preponderance of methicillin resistance; vancomycin can be used as a presumptive treatment of BSI in neutropenic patients suffering from the hematological disorders. There are some drawbacks of the present study that we used only conventional biphasic media. The sensitivity of the blood culture, in such patients, may be enhanced by the use of continuous monitoring blood culture systems (CMBCS). In present study, we didn't isolate a single fungus, which can be improved by the molecular diagnostics as the culture negative BSI are considered to be a fungal origin. Apart from these, we only focused on the blood-stream infection, keeping the other respiratory, urinary and gastrointestinal infection, sideways.

## CONCLUSION

Staphylococci are the predominant cause of blood stream infection among neutropenic patients, suffering from hematological disorders. Most of the Staphylococci, being methicillin-resistant, are resistant to the all  $\beta$ -Lactam group of antibiotics. In such cases, vancomycin can be used an empirical treatment. Gram-negative bacteremia, in these patients, is usually caused by drug resistant microbes which necessitate the blood culture & sensitivity in each case of blood stream infection among the neutropenic patients suffering from hematological disorders.

## REFERENCES

1. Steven MH, John IG (2008) Disorders of granulocytes and monocytes, chapter 61. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL (eds) Harrison's principles of internal medicine, 17th edn. Macgraw-Hill Book Co, Singapore, pp 375-384
2. Bos MM, Smeets LS, Dumay I, De Jonge E. Bloodstream infections in patients with or without cancer in a large community hospital. *Infection*. 2013 Oct 1;41(5):949-58.
3. Klustersky J, De Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, Herrstedt J. Management of febrile neutropaenia: ESMO clinical practice guidelines. *Annals of Oncology*. 2016 Sep 1;27(suppl\_5):v111-8.
4. Meunier F (2004) Infections in patients with acute leukemia and lymphoma, chap 288. In: Mandell GL, Bennetts JE, Dolin R (eds) Mandell, Douglas & Bennett's principles & practice of infectious disease, 6th edn. Churchill Livingstone, Philadelphia, PA, pp 2666-2675

5. Ibrahim TM, Pang C. Bacteremia Pattern in Febrile Neutropenia among Adults Cancer Patients Receiving Chemotherapy in an Australia Regional Hospital. *Universal Journal of Public Health* 2017;5(4): 172-175
6. Morris PG, Hassan T, McNamara M, Hassan A, Wüig R, Grogan L, Breathnach OS, Smyth E, Humphreys H. Emergence of MRSA in positive blood cultures from patients with febrile neutropenia—a cause for concern. *Supportive care in cancer*. 2008 Sep 1;16(9):1085-8.
7. Collee, J.G., Duguid, J.P., Fraser, A.G., Marmion, B.P., Simons, A. 2012. Laboratory strategy in the diagnosis of infective syndrome- Chapter 4. Mackie and McCartney *Practical Medical Microbiology*; 14th ed. Churchill Livingstone Elsevier, London, UK, 62-6
8. Fernandes CJ, Fernandes LA, Collignon P. Cefoxitin resistance as a surrogate marker for the detection of methicillin-resistant *Staphylococcus aureus*. *Journal of Antimicrobial Chemotherapy*. 2005;55(4):506-10.
9. Laboratory Clinical Standards Institute (CLSI) (2006) Performance standards for antimicrobial susceptibility testing. CLSI approved standard M-100-S16 (M7). Clinical and Laboratory Standards Institute, Wayne, PA
10. Babu KG, Lokanatha D, Lakshmaiah KC, Babu MS, Jacob LA, Bhat GR et al. Bloodstream infections in febrile neutropenic patients at a tertiary cancer institute in South India: A timeline of clinical and microbial trends through the years. *Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical & Paediatric Oncology*. 2016 Jul;37(3):174.
11. Pasqualotto AC, Rosa DD, Medeiros LR, Severo LC. Candidaemia and cancer: patients are not all the same. *BMC infectious diseases*. 2006 Dec;6(1):50.
12. Rosenblum J, Lin J, Kim M, Levy AS. Repeating blood cultures in neutropenic children with persistent fevers when the initial blood culture is negative. *Pediatric blood & cancer*. 2013 Jun;60(6):923-7.
13. Horasan ES, Ersoz G, Tombak A, Tiftik N, Kaya A. Bloodstream infections and mortality-related factors in febrile neutropenic cancer patients. *Medical science monitor: international medical journal of experimental and clinical research*. 2011;17(5):CR304.
14. Lamoth F, Jatou K, Prod'homme G, Senn L, Bille J, Calandra T, Marchetti O. Multiplex blood PCR in combination with blood cultures for improvement of microbiological documentation of infection in febrile neutropenia. *Journal of clinical microbiology*. 2010 Oct 1;48(10):3510-6.
15. Scheer CS, Fuchs C, Gründling M, Vollmer M, Bast J, Bohnert JA, Zimmermann K, Hahnenkamp K, Rehberg S, Kuhn SO. Impact of antibiotic administration on blood culture positivity at the beginning of sepsis: a prospective clinical cohort study. *Clinical Microbiology and Infection*. 2018 Jun 4.
16. Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. *Journal of postgraduate medicine*. 2001 Apr 1;47(2):104.
17. Choo EJ, Chambers HF. Treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Infection & chemotherapy*. 2016 Dec 1;48(4):267-73.
18. Fowler VG, Sexton DJ. Clinical approach to *Staphylococcus aureus* bacteremia in adults. *UpToDate*. Waltham, MA: Wolters Kluwer. 2013.