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*Original Article*

# Bacterial profile and antibiogram of blood stream infections in febrile neutropenic patients with haematological malignancies

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## Abstract

Introduction: Studies have shown a shift in the prevalence from Gram-positive to Gram-negative bacteraemia in patients with haematological malignancies who develop febrile neutropenia. There are also reports on the spread of drug resistant bacteria among these patients. Information about locally prevalent bacteria and their resistance is important to guide empirical therapy. The aim of this study was to characterise the bacterial spectrum and antibiotic resistance pattern of bacteraemia in neutropenic patients with haematological malignancies

Methodology: In this retrospective study, patients admitted to Haematology and Oncology units over a period of 6 months with laboratory-confirmed positive blood cultures were enrolled. Information regarding demographic profile, clinical features, and microbiological profile were recorded. Standard procedures were applied to identify the isolates and their resistance patterns. The data collected was analysed statistically.

Results:56 isolates from 53 patients were isolated of which majority were gram negative bacilli (GNB; n = 52 or 93%). *Klebsiella pneumoniae* (43%, n = 24) was the most frequently isolated bacteria followed by *Enterobacter sp* (20%, n = 11) and *Escherichia coli* (12%, n = 7). All isolates were susceptible to colistin. Susceptibility to cefaperazone-sulbactam, piperacillin-tazobactam and carbapenems were 32%, 28.6% and 26.8% respectively. The outcome was fatal for 25 patients.

Conclusions: The study documented an alarming rise in the prevalence of GNB and their resistance. Though the results of the study may represent only the tip of the iceberg, the results demonstrate the need for treatment options for drug resistant isolates and for surveillance cultures.

**Key words:** bloodstream infection; *Klebsiella pneumoniae*; antibiotic resistance; febrile neutropenia; haematological malignancy.

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## Introduction

Bloodstream infections (BSIs) are a major cause of morbidity and mortality in cancer patients. These infections occur frequently in patients who develop febrile neutropenia (FN) during chemotherapy and after bone marrow transplant [1]. The reported prevalence of BSIs in patients with haematological malignancies ranges from 11-38%, with crude mortality rates reaching 40% [2]. Prompt institution of appropriate empirical antibiotic therapy can help decrease mortality rates in these patients [3].

In the late 1970s and early 1980s, GNB were the predominant cause of BSIs in neutropenic patients [1]. Increased use of prophylactic fluoroquinolones, long term indwelling catheters, and use of antacids led to an increase in Gram-positive bacteraemia in the 1990s [1]. In recent years, several studies have reported a shift in prevalence from Gram-positive to Gram negative bacteraemia [2]. Accompanying this shift is the rise and successful dissemination of multi drug resistant (MDR), extensively drug resistant (XDR) and pan drug resistant (PDR) gram negative bacteria [4].

In view of this dynamic change in epidemiology, information about the locally prevalent pathogens and their resistance patterns is of utmost importance to decide appropriate empirical therapy.

The present study was undertaken to evaluate the current microbiological spectrum and antibiotic resistance pattern of BSIs in neutropenic patients with haematological malignancies at a tertiary care centre.

## Methodology

*Patient profile*

This retrospective study was conducted over a period of six months (1st July 2014 – 31st December 2014) at a tertiary care hospital in New Delhi, India.

Patients admitted to the Oncology units with haematological malignancies and febrile neutropenia were enrolled in the study. Patients were included if they had

a) fever defined as a single oral temperature of ≥ 38.3°C or a temperature of ≥ 38°C lasting for one hour
b) neutropenia defined as an absolute neutrophil count of < 500 cells/mm$^3$ and
c) laboratory confirmed blood stream infection.

All medical records of the enrolled patients were reviewed in detail and vital information was recorded in a specific database. These included demographic data, baseline characteristics, clinical features, empirical antibiotic therapy, microbiological results and treatment outcome.

*Microbiological analysis*

A minimum of two samples were collected from each patient and incubated in blood culture bottles. Subcultures were made onto blood agar (Biomerieux, Paris, France) and MacConkey agar (HiMedia, Mumbai, India). The isolates were identified on the basis of their gram stain, colony morphology and standard biochemical reactions. Antibiotic susceptibility testing was performed using the Kirby Bauer disc diffusion method according to the CLSI guidelines. ATCC control strains were used to ensure the quality of each procedure [5].

Each incident of FN was treated as a separate episode. An episode of bacteraemia was defined as ≥ one blood culture yielding a pathogen, with the exception of coagulase-negative staphylococci (CoNS), for which isolation from two blood culture samples was considered significant. When only a single blood sample was available isolation of CoNS was considered significant if the patient had consistent clinical parameters [6].

For fungal culture, samples were inoculated into Sabouraud dextrose agar (Merck, Mumbai, India,) with chloramphenicol and cycloheximide (Sigma-Aldrich Corp., St. Louis, USA). Isolates were identified using Lactophenol cotton blue mount. Galactomannan assay was performed for serum samples using Platelia *Aspergillus* EIA (Bio-Rad, Marnes-la-Coquette France). Fungal infections were defined according to the EORTC/ MSG guidelines [7].

*Statistical analysis*

All data collected were analysed using IBM SPSS (version 20). Univariate analysis was performed for gender, type of malignancy, type of treatment, profound

**Table 1.** Demographic profile of patient population.

| Patient characteristic | | n (%) |
|---|---|---|
| Gender | Male | 37 (70) |
| | Female | 16 (30) |
| Haematological malignancy | Acute myeloid leukaemia | 25 (47) |
| | Acute lymphocytic leukaemia | 9 (17) |
| | Non-Hodgkin's lymphoma | 8 (15) |
| | Hodgkin's lymphoma | 5 (9) |
| | Others | 6 (11) |
| Disease status | Active | 37 (70) |
| | Remission | 6 (11) |
| | Relapse | 10 (19) |
| Treatment | Primary chemotherapy | 34 (64) |
| | Salvage chemotherapy | 5 (9) |
| | Bone marrow transplant | 14 (26) |
| Co-morbidities | Diabetes mellitus type 2 | 4 (8) |
| | Hypertension | 2 (4) |
| | Tuberculosis | 2 (4) |
| | Others | 1 (2) |
| Other foci of infection | Lower respiratory tract | 21(40) |
| | Catheter related | 10 (19) |
| | Gastrointestinal tract and perianal | 10 (19) |
| | Urinary tract | 5 (9) |
| | Skin and soft tissue | 1 (2) |
| Invasive fungal infection | Proven | 0 |
| | Probable | 14 (26) |
| | Possible | 7 (13) |

neutropenia, type of stem cell transplant, pneumonia, invasive aspergillosis, and bacteria isolated, to determine their association with outcome.

## Results

*Patient profile*

Fifty-three patients admitted to the oncology unit during a 6-month period were included in the study. They were diagnosed with various haematological malignancies with febrile neutropenia and blood stream infections. Demographic details have been provided in the table (Table 1).

The most common haematological malignancy among the patients was acute myeloid leukaemia (AML; n = 25) followed by acute lymphoblastic leukaemia (ALL; n = 9), Non-Hodgkins lymphoma (n = 8) and Hodgkins lymphoma (n = 5). More than two thirds of the patients had active disease at the time of infection while ten had suffered a relapse. A slight majority of the patients were receiving primary chemotherapy. Fourteen patients had received a stem cell transplant, of which seven were autogenous and the others were allogeneic. A few patients had co-morbidities details of which are provided in the table (Table 1).

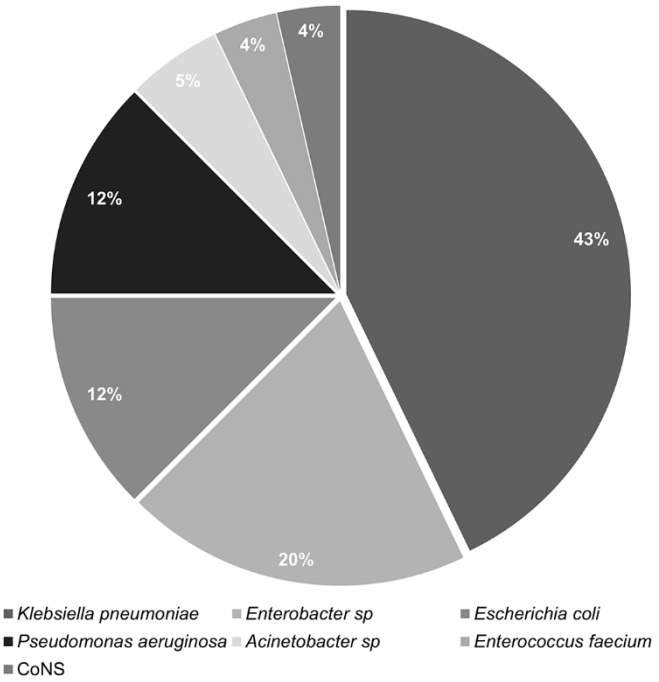
*Microbiology results*

Though 76 episodes of febrile neutropenia were recorded in these 53 patients during the study period, only 53 episodes were associated with a blood stream infection. In 50 episodes a single pathogen was isolated while for three episodes two pathogens were isolated.

Nearly all of the 56 isolates, were GNB, and nearly half were *K. pneumoniae* (n = 24; 43%) making them the most frequently isolated bacteria, followed by *Enterobacter* sp at 20%, *Escherichia coli* and *Pseudomonas aeruginosa* at just over 10%, and *Acinetobacter* sp in three patients. A few Gram-positive bacteria were also isolated: *Enterococcus faecium* and CoNS each in two cases (Figure1).

Thirty-eight patients in the study group had other identifiable clinical foci of infection. The most common site involved was the lower respiratory tract followed by line related infections, GIT and perianal infections and urinary tract infections Microbial documentation of infection was possible in 19 episodes. Among these, in five episodes the same organism was isolated in blood as from the other clinical foci. *Enterobacter* sp was isolated in two episodes of urinary tract infection and BSI. *E. coli* was isolated in an episode of urinary tract infection and BSI. *Enterobacter* sp and *K. pneumoniae* caused bacterial pneumonia and BSI in two episodes

**Figure 1.** Distribution of bacterial isolates.




According to EORTC/MSG guidelines, 14 cases had probable invasive fungal infections and 7 had possibly invasive fungal infections (Table 1).

*Antibiotic sensitivity*

*K. pneumoniae*, *Enterobacter* sp, *Escherichia coli* and *Pseudomonas aeruginosa* accounted for 92% of the isolates. The CoNS isolated in the study were sensitive to methicillin. *Enterococcus faecium* isolates were sensitive to vancomycin and teichoplanin. All the GNB were susceptible to colistin. Overall, around one third of isolates showed susceptibility to cefaperazone-sulbactam and slightly fewer to piperacillin tazobactam and carbapenems. Susceptibility to the aminoglycosides amikacin and netilmycin were lower at between 10 and 15%.

*K. pneumoniae* demonstrated a low susceptibility to cefaperazone-sulbactam, piperacillin tazobactam, carbapenems and aminoglycosides All the *Enterobacter* sp isolates were resistant to the beta lactam beta lactamase inhibitor combinations and aminoglycosides. They also showed a low susceptibility to carbapenems. However, the *E. coli* and *P. aeruginosa* isolates had a higher susceptibility to beta lactam beta lactamase inhibitor combinations. While *E. coli* demonstrated a high susceptibility to carbapenems only 14% of the *P. aeruginosa* isolates were sensitive to the same (Table 2)

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**Table 2.** Antimicrobial susceptibility pattern of isolated GNB.

| Organism | Antibiotics (% susceptible isolates) | | | | | |
|---|---|---|---|---|---|---|
| | Cefaperazone-sulbactam | Piperacillin - tazobactam | Imipenem | Amikacin | Ceftazidime | Ciprofloxacin |
| *Klebsiella pneumoniae* (n = 24) | 7 (29%) | 5 (21%) | 5 (21%) | 2 (8%) | 0 | 2 (8%) |
| *Enterobacter* spp (n = 11) | 0 | 0 | 2 (17%) | 0 | 0 | 0 |
| *Escherichia coli* (n = 7) | 5 (71%) | 5 (71%) | 6 (86%) | 3 (43%) | 0 | 0 |
| *Pseudomonas aeruginosa* (n = 7) | 4 (57%) | 4 (57%) | 1 (14%) | 1 (14%) | 2 (29%) | 2 (29%) |

*Factors associated with outcome*

Outcome was fatal for 25 of the 53 patients. For eight of them, the cause of death was septic shock. Four of these patients had blood stream infection by *K. pneumoniae*, three by *Enterobacter* sp and one by *Escherichia coli*. While comparing the isolated pathogens and outcome, it was found that twelve patients (48%) with *K. pneumoniae* had a fatal outcome followed by *Enterobacter* sp (n = 8; 32%) and *E. coli* (n = 2; 8%). Patients diagnosed with AML had the highest mortality followed by patients with lymphomas. To identify significant association between various risk factors and outcome, univariate analysis was performed. A significant association was found only for profound neutropenia and fatal outcome ($p \leq 0.046$).

## Discussion

Blood stream infections are an important cause of morbidity and mortality in cancer patients with neutropenia [1]. Such infections may be curtailed by prescribing appropriate empirical antibiotics based on the antibiotic resistance pattern in the hospitals [3]. Routine surveillance for multi drug resistant organisms is also important, since emergence of resistant bacteria is associated with increases in treatment failures, hospital costs and mortality [2]. The present study was undertaken to identify the profile of the different bacterial agents causing BSIs in neutropenic patients. The study also investigated possible risk factors for mortality among these patients.

Gram-positive cocci (GPC) were earlier reported to be the most common cause of BSIs in neutropenic patients [1]. But several studies in recent years have noted a shift of prevalence from GPC to GNB [2]. The centre where the present study was undertaken had reported increasing prevalence of GNB among neutropenic patients with BSI since 2000. Mathur *et al.* in 2002 and Ghosh *et al.* in 2012 reported 47% and 56% GNB respectively among the isolates in their studies [8,9]. However, the present study documented a much higher prevalence of GNB (91%). This increase may be attributed to one or more of the following: the discontinuation of fluoroquinolone prophylaxis in our centre, chemotherapy-associated mucositis, use of long term indwelling catheters, and immune defects like neutropenia and lymphocyte dysfunction [9,10].

Many international studies on the bacterial spectrum of BSIs in neutropenic patients found *E. coli* to be the most frequently isolated bacteria followed by *P. aeruginosa, K. pneumoniae* and Acinetobacter [2]. Similar results were found in our study site by Mathur *et al*. in 2002 [8]. A 2012 study by Ghosh *et al*. identified *P. aeruginosa* as the most common isolate followed by *E. coli*, *Acinetobacter* and *K. pneumoniae* [9]. However, in the present study *K. pneumoniae* was the most frequently isolated bacteria followed by Enterobacter sp (20%), *Escherichia coli* (12%) and *Pseudomonas aeruginosa* (12%). The rise of *K. pneumoniae,* especially drug resistant isolates, has been documented by Satlin *et al.* and Micozzi *et al.* in recent studies [11,12].

An increase in the antibiotic resistance rates in isolates has been documented from patients with hematological malignancies and febrile neutropenia in several studies. A study by Babu *et al.* in 2016 demonstrated 62% sensitivity to cefaperazone-sulbactam and 70 % sensitivity to carbapenems [13]. Similarly, a high level of susceptibility to cefaperazone-sulbactam (84%), piperacillin tazobactam (66%) and carbapenems (64%) was observed in an earlier study from the same institute [9]. These results are in contrast to the findings of the present study. According to the definitions of drug resistance set by Magiorakis *et al.*, most of the isolates in this study are multidrug resistant or MDR and 49% of the isolates fulfil the definition criteria for XDR or extensively drug resistant isolates [14]. Reddy *et al.* analysed 412 blood cultures among paediatric patients with malignancy from the same centre where the present study took place. They found a similar predominance of drug resistant *K. pneumoniae* among paediatric patients [15]. However, the present study, which looked at BSIs in all febrile neutropenic

patients including 15 paediatric cases during a span of 6 months, noted a higher number of BSIs, a higher incidence of XDR isolates as well as a higher fatality rate among the patients.

The alarming development of resistance to beta lactam beta lactamase inhibitor combinations and carbapenems in the present study is a direct result of increase in the prevalence of resistant Enterobacteriaceae like *K. pneumoniae* and *Enterobacter* sp. Worldwide, several reports have appeared on the emergence of carbapenem resistant Enterobacteriaceae especially *K. pneumoniae* causing infection in cancer patients [4,11,12].Carbapenem resistant *K. pneumoniae* and Enterobacter have even caused outbreaks leading to BSI and death in cancer patients [16]. Patients with haematological malignancies are particularly vulnerable to these infections because of the above-mentioned risk factors [10]. The irrational use of broad spectrum antibiotics as well as prolonged hospitalisation may both add to the risk of acquiring infections by drug resistant bacteria. These pathogens are usually endogenous. Broad spectrum antibiotics given as treatment or prophylaxis exert selection pressure leading to the survival of resistant strains of bacteria, particularly in the gut [17]. Nouer *et al.* described how patients with haematological malignancies undergo repeated cycles of chemotherapy and receive broad spectrum antibiotics with each cycle, which provides a suitable environment for selection pressure [17]. This is especially noteworthy since during the study period, cefaperazone- sulbactam was empirically prescribed as the first line antibiotic followed by carbapenem and colistin. Other factors, like the use of antibiotics in agricultural products and poultry as well as in antibacterial soaps and gels, also contribute to the spread of drug resistant bacteria even in the community [18].

The fatality rate among the patients in our study was high (47%). An attempt was made to identify possible risk factors associated with mortality. Though *K. pneumoniae* was the most common isolate, its prevalence was not found be associated with mortality. Similarly, AML was the most common malignancy in the study group, but no association with fatality was detected. Profound neutropenia was the only factor that showed a significant association with mortality. This may be because neutropenic episodes pose a higher risk for acquiring infections caused by drug resistant bacteria [19].

The present study had its limitations. The study was retrospective and covered a small study population over a span of 6 months. This reduced the probability of identifying risk factors for mortality. A more elaborate prospective study may be required to understand in depth the roles of drug resistance and associated risk factors. However, the study documented an increase in the prevalence of GNB isolates among febrile neutropenic patients with BSI, and noted an alarming increase in resistance among these isolates as well in the mortality among the patients. These results suggest that treatment options, especially for the XDR isolates, should be reconsidered. Searching for other infectious foci and controlling them is also important to control infections by drug resistant bacteria. As suggested by Averbuch *et al.*, one approach to reduce the spread of resistant bacteria may be to introduce surveillance in the form of rectal swabs at the time of admission in patients with history of prolonged or previous hospitalisation [20].

## Conclusion

BSIs are an important cause of mortality and morbidity in febrile neutropenic patients with haematological malignancies. Studies have documented a shift in prevalence from Gram-positive to gram negative bacteraemia as well as the rise and spread of drug resistant bacteria in these patients. Due to this dynamic epidemiology, knowledge about prevalent bacteria and their antibiogram is essential to guide empirical therapy. The present study demonstrated an alarming rise in the prevalence of drug resistant GNB as well as mortality among these patients. *K. pneumoniae* and *Enterobacter* sp were the predominant isolates. Whereas *K. pneumoniae* demonstrated a low susceptibility to cefaperazone-sulbactam, carbapenems and aminoglycosides all the *Enterobacter* sp isolates were resistant to the beta lactam beta lactamase inhibitor combinations and aminoglycosides and showed a low susceptibility to carbapenems. The study also had a high number of XDR isolates These results demonstrate the need for surveillance cultures and alternate treatment options for XDR isolates in such patients.

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