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Research Article

Institutional Sensitivity Pattern Guides Initial Antimicrobial Selection in Febrile Neutropenia; Sharing Experience from a Hemato-Oncology Care Center in India

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Abstract

Background: Febrile Neutropenia (FN) is the common cause of morbidity and mortality in hematological malignancy, especially in developing countries.

Aims and objectives: To evaluate the clinical characteristics, understand the pattern of BSI, antimicrobial sensitivity pattern and to determine the evidence based empirical therapy in FN.

Methods: Present study conducted in 710 patients suffering from different types of hematological malignancies. The blood samples from central and peripheral veins collected during episodes of febrile neutropenia, cultured by BACTEC method (Aerobic and Anaerobic); in some cases (where clinically indicated) CVC tip sent for culture sensitivity. Blood agar, chocolate agar, MacConkey agar, Nutrient agar and SDA were used for isolation of the microorganisms.

Results: Out of 1664 cases of FN episodes, positive culture report was obtained in 499 (30.05%) episodes. GNB isolated in 67.1% (335/499) cases, GPB in 29.5% (147/499) cases and in 3.4% (17/499) cases fungal spp. were isolated. Most common species isolated was *Klebsiella pneumoniae* in 32.3% (161/499) followed by CoNS in 15.4% (77/499) episodes. Among fungal infections, *Candida albicans* was the commonest (n=14/17). Average FN episode per patient was high in AML (3.2) followed by BL (2.6) and APL (2.12). Majority among GNBs and GPBs had shown high sensitivity (90% to 100%) to carbapenems and aminoglycosides in comparison to low to moderate sensitivity (40% to 90%) to pip-tazo and cefepime.

Conclusion: Based on the current trends in micro-organisms isolated and the sensitivity pattern, every hemato-oncology care hospital should preferably have their own institutional antibiotic policy for improved patient care.

Keywords: Hematological malignancy; Febrile neutropenia; Micro-organisms isolated; Antimicrobial sensitivity; Institutional policy

Abbreviations

FN: Febrile Neutropenia; SDA: Sabouraud Dextrose Agar; GNB: Gram Negative Bacteria; CVC: Central Venous Catheter; CoNS: Coagulase Negative *Staphylococci*; AML: Acute Myeloid Leukemia; DLBCL: Diffuse Large B Cell Lymphoma; BL: Burkitt Lymphoma; NHL: Non Hodgkin Lymphoma; APL: Acute Promyelocytic Leukemia; IDSA: Infectious Diseases Society of America; BSI: Blood Stream Infection; G-CSF: Granulocyte Colony Stimulating Factor; Cef-Sul: Cefoperazone/Sulbactam; Pip-Tazo: Piperacillin/Tazobactam; Amoxy-clav: Amoxicillin/Clavulanic Acid; MASCC: Multinational Association for Supportive Care in Cancer

Introduction

Febrile Neutropenia (FN), defined as per IDSA guidelines 2010 [1]; fever defined as single oral temperature of ≥ 38.3°C or oral temperature of ≥ 38.0°C that persists for over 1 h, neutropenia defined as an absolute neutrophil count (ANC) of ≤ 500 cells/mm^3. FN may occur within 7-12 days following cancer chemotherapy, depending upon the type of disease and chemotherapeutic agent(s) used [2]. FN is a common complication in patients on immunosuppressive therapy for any cause such as acute leukemia and many other hematological malignancies, bone marrow transplantation and in aplastic anemia [3]. Febrile neutropenia is associated with a high morbidity and mortality [1]. In febrile neutropenic patients, the rate of Blood Stream Infection (BSI) is reported to be between 5 and 48% [4,5]. BSI is a significant cause of morbidity and mortality among the neutropenic patients, suffering from hematological malignancies [6,7]. Knowledge of prevalent organism and sensitivity pattern plays a very important role in reducing morbidity and mortality in hematological malignancy patients with treated with cancer chemotherapy; high index of suspicion and early empirical antibiotics are the most important interventions to reduce high mortality for these patients [8].

The purpose of this prospective observational study was to evaluate the clinical characteristics, understand the pattern of BSI, antimicrobial sensitivity pattern and to determine the evidence based empirical therapy in FN.

Patients and Methods

A prospective observational study conducted among the patients of all age groups with hematological malignancy admitted at hematology department, NRS Medical College and Hospital over a period of four and half years between July, 2015 and December, 2019. Blood specimens were taken in patients with FN as per IDSA 2010 guidelines after taking informed and written consent. One set

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of blood cultures were collected, simultaneously from each lumen of an existing CVC, if present and also from a peripheral vein site; 2 blood culture sets from separate venepunctures were sent if no CVC was present. Samples were collected in BCTEC culture bottle (both aerobic and anaerobic), volumes limited to <1% of total blood volume of the individual patient under study [1]. Fresh blood culture samples drawn during recrudesce of fever. The medical history including diagnosis, chemotherapy used, relapse, duration and severity of neutropenia, use of G-CSF, prophylactic antibiotics or antifungal agents, other infection related factors, i.e., antifungal therapy for a probable or proven fungal infection within past 6 months were noted carefully. Culture and sensitivity testing was done in the Department of Microbiology, NRS Medical College and Hospital; organisms were identified by Gram stain, motility tests and biochemical reactions as per standard protocol following culture [9,10]. Blood agar, chocolate agar, MacConkey agar, Nutrient agar and SDA were used for isolation of the microorganisms. The antimicrobial susceptibility tests were done by Kirby Bauer's disc diffusion method on Mueller-Hinton agar and interpreted as per CLSI guidelines, 2010 [10]. Standard antibiotic discs (HiMedia, Mumbai, India) used as shown in detail in the results section. Statistical analyses were performed with STATA™ Software (StataCorp LLC, USA).

Results

Analysis of all FN episodes in 710 patients suffering from different types of hematological malignancies (Table 1) was done. Total 1664 episodes of FN noted according to different types of hematological malignancies; average FN episode per patient was 2.34 (1664/710), that was highest in patients with AML (3.2) followed by Burkitt lymphoma (2.6), APL (2.12), DLBCL (1.9) and ALL (1.9). Out of 1664 FN episodes, positive culture report was obtained in 499 (30.05) episodes. Predominant organism isolated were GNB in 67.1% (335/499) cases followed by GPB in 29.5% (147/499) cases and fungal spp. in 3.4% (17/499) cases. As shown in Figure 1, among GNBs, the most common microorganism species isolated was *K. pneumoniae* in 32.3% (161/499) followed by *Acinetobacter* spp. in 14.8% (74/499), *Pseudomonas aeruginosa* in 14.4% (72/499) and *Burkholderia* spp. in 3.2% (16/499) episodes of FN. Among 74 isolates of *Acinetobacter* spp., *A. baumannii* found in 73 cases and in only one case it was *A. lwoffii*. The most common GPB isolated was CoNS in 15.4% (77/499) episodes followed MRSA in 7.4% (37/499) and MSSA in 4.4% (22/499) episodes. *Candida albicans* predominated (82.3%, n=14/17) among different fungal strains isolated.

The antibiotic sensitivity patterns of different GNBs are shown in Figure 2. The most common GNB isolate *K. pneumoniae* had shown very good *in vitro* sensitivity to carbapenems followed by colistin/polymixin B, aztreonam, pip-tazo and poor sensitivity to cefepime and tigecycline. *Pseudomonas aeruginosa* had shown excellent sensitivity to amikacin and carbapenems followed by pip-tazo, tigecycline, aztreonam and colistin/polymixin B but poor sensitivity to cefepime, ciprofloxacin, gentamicin. *Acinetobacter* spp., another dominant GNB isolated in the study had shown very good sensitivity to cefuroxime, ciprofloxacin, carbapenems, aminoglycosides, pip-tazo followed by cefepime, colistin/polymixin B and poor sensitivity to cefsul and tigecycline. *Buspholderia* spp., the next dominant organism isolated in the study had shown good sensitivity pattern to imipenem followed by colistin, aztreonam and amikacin. As shown in Figure 3, the most common GPB, Coagulase negative *Staphylococci* had shown very good *in vitro* sensitivity to Aminoglycosides, Vancomycin, Teicoplanin, Tigecycline followed by Meropenem and Pip-Tazo. *Staphylococci* spp. as a whole had shown good sensitivity to Vancomycin, Teicoplanin, gentamicin, Tigecycline followed by Meropenem and Pip-Tazo. Sensitivity pattern of fungal isolates are shown in Figure 4. *C. albicans* had shown almost similar *in vitro* sensitivity pattern to fluconazole, voriconazole, amphotericin B, caspofungin followed by posaconazole. Among non-albicans isolates, *C. glabrata* had shown good sentivity to all except caspofungin and *C. parapsilosis* had shown very poor sensitivity to fluconazole.

Discussion

Febrile Neutropenia (FN) is an oncological emergency. Depending on degree and severity of neutropenia, patients with hematological malignancies are highly vulnerable to both bacterial and fungal infections; mortality rates exceed 50% in patients presenting with septic shock or pneumonia, despite prompt antibiotic treatment [7,11]. Blood culture is routinely done to determine the causative agent of BSI; sensitivity range from 15% to 25%; poor sensitivity of the blood culture may be attributed to non-infectious origin of fever [7]. Repeat blood culture is executed if initial report becomes negative; bacteremia detected in >10% of FN episodes if repeat blood culture is obtained, despite an initial negative report [12]. In the present study, positive culture report obtained in 30.05% (499/1664) FN episodes. Babu KG et al. [6] from a tertiary cancer institute in South India, reported culture positivity in 13% (137/887) episodes and Gupta MK et al. [13] from North India reported culture yield in 27% (27/100) episodes. In 1960s to 1970s, GNB were more predominant causative agents in FN; there is changing trend from GNB to GPB due to widespread use of prophylactic antimicrobial agents mainly active against GNB and also increased use of CVCs [14]. In many other small studies including one by Gupta MK et al. [13] had shown Staphylococci (n=23/27) were the most frequent isolate from the Blood. Siddiqui B et al. [5] shared experience of BSI in FN episodes from a developing country (Pakistan) and reported the frequency of *S. aureus* in 16% followed by *Klebsiella*, *E. coli* and *Pseudomonas* in 15.5%, 14.5% and 8.5% respectively. However, the present study (Figure 1) revealed GNB predominance (67.1%) among all culture

Table 1: Distribution of patients according to type of hematological malignancies, episodes of febrile neutropenia and blood culture yield.

Disease entity	Total patients (n)	FN episodes (n)	Average no. of FN episode per patient	Culture positivity n (%)	GPB growth (n)	GNB growth (n)	Total Fungi isolated (n)
AML	240	770	3.2	260 (33.7)	75	181	4
DLBCL	26	50	1.9	15 (30)	4	9	2
BL	15	40	2.6	14 (35)	3	10	1
MDS	12	18	1.5	6 (33.3)	2	4	0
MM	32	52	1.6	7 (13.5)	2	4	1
Other NHL	38	60	1.5	10 (16.6)	3	5	2
APML	55	117	2.12	39 (33.3)	15	23	1
ALL	292	557	1.9	148 (26.6)	43	99	6
Total	710	1664	2.34	499 (30.05)	147	335	17

isolates and *K. pneumoniae* (32.3%) was the most common organism identified. Among GPBs (29.5%), CoNS (15.45%) was the most common predominantly identified. In a retrospective study carried out during 2003-2010 in the clinical hematology unit, Bousquet A et al. [15] had shown predominance of GNB (70.8%) over GPB (18.7%). In another study by Braun E et al. [16], on epidemiology of Catheter-Related Bloodstream Infections (CRBSIs) between 1996 and 2012 with a cohort of 1754 episodes, had shown a shift from GPB to GNB in the current years (In 1996; 68% CRBSIs caused by GPB whereas in 2012, GNBs isolated in 77.8% episodes). In a prospective study conducted over 3 years from September'2010 to October'2013 by Mandal PK et al. [17] from Eastern India reported culture positivity of 29.10% (78/268) with dominance of GNBs (61.53%) over GPBs (34.61%). As shown in Table 1, average FN episodes per patient were highest in patients with AML that can be explained by prolonged and profound neutropenia associated with chemotherapy. GNBs predominated across the types of all hematological malignancies especially in AML, BL and ALL cases.

In the present study, among GNBs (Figure 1), *K. pneumoniae* (32.3%, n=161/499) was the most common isolate followed by *Acinetobacter* spp. (14.8%, n=74/499) and *P. aeruginosa* (14.4%, n=72/499). In the study by Braun E et al. [16], *P. aeruginosa* (22%) was the commonest isolate followed by *Klebsiella* (19.5%) and Bousquet A et al. [15] had shown most common species isolated was *E. coli* (18.5%) followed by *P. aeruginosa* (14.8%). In the study by Mandal PK et al. [17] in 2010 to 2013 from the present institute had shown *P. aeruginosa* (14.10%) was the most common GNB isolated followed by *Acinetobacter* spp. (11.53%), *E. coli* (8.97%) and *K. pneumonia* (8.97%). Thus studies during same time frame from different centers [15-17] show dominance of different microbial agents and even in the same center there is a shift in microbial patterns as reflected in the present study when compared to the previous one [17].

The four common GNBs isolated had shown very good *in vitro* sensitivity (Figure 2) to carbapenems (90% to100%) and amikacin (80% to100%) in comparison to low sensitivity with colistin/ polymixin B (80% to 90%) and pip-tazo (70% to 90%). *Acinetobacter* spp., an emerging multidrug resistant BSI was an significant isolate in the present study that showed good sensitivity (100%) to cefuroxime, ciprofloxacin, carbapenems, amikacin (90%) in comparison to pip-tazo and cefepime (80% in both cases) that showed good efficacy in clinical use of oral cefuroxime and ciprofloxacin in addition to other sensitive drugs. In a study [18] from All India Institute of Medical Sciences, New Delhi, India analyzing for BSIs showed predominance of gram negative organism (72.9%, n=78/105) with *Acinetobacter* spp. emerging as common (18.7%, n=20/105) pathogen and displayed very high resistance to major classes of antibiotics, including multidrug resistance. *Burkholderia* spp. constitutes (3.2%) fourth important isolate in this study and had shown good sensitivity to imipenem followed by colistin, aztreonam and amikacin and poor sensitivity to pip-tazo (70%) and cefepime (40%). Baul SN et al. [19] recently reported an outbreak of *B. cepacia* infection where it showed resistance to most of the antibiotics in hospitalized patients including pip-tazo, cefepime and amikacin; it is a frequent colonizer of fluids used in the hospital wards; is a known important opportunistic pathogen causing morbidity and mortality due to its intrinsic resistance to antibiotics and change of antibiotic preparation practice was the key to control the outbreak, and overall mortality was low. Trecarichi EM et al. [20] from an Italian multicentre prospective survey on antimicrobial resistance for BSI in patients with hematologic malignancies revealed major concern of antimicrobial resistance among Gram-negative bacteria.

Among GPBs in the present study (Figure 3), CoNS found in 15.4% (77/499) followed by *S. aureus* in 11.8% (59/499) episodes. CoNS had shown very good (90% to100%) *in vitro* sensitivity to carbapenems, aminoglycosides, vancomycin, tigecycline, clindamycin followed by moderate sensitivity to Meropenem (80%) and Pip-Tazo (70%). *Staphylococci* spp. as a whole again showed very good sensitivity (90% to 100%) to aminoglycosides, vancomycin, meropenem followed by Pip-Tazo (80%). showed resistance too many antibiotics except aminoglycosides, vancomycin and tigecycline. Trecarichi EM et al. [20] reported >92% of *staphylococci* and *enterococci* susceptible to glycopeptides in their cohort. Gupta MK et al. [13] from North India reported excellent sensitivity in all GPB isolates to vancomycin and linezolid in contrast to the present study where both *Enterococcus* spp. and *S. pneumoniae* has shown resistance to these drugs in a significant proportion. The present study revealed MRSA in 62.7% (n=37/59) as compares to their study (65.2%, n=15/23).

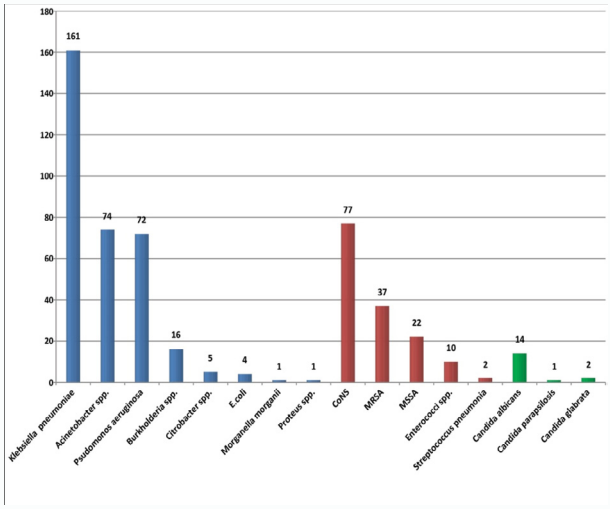

Figure 1: Distribution of Gram negative bacteria (blue), Gram positive bacteria (red) and fungi (green) isolated (n=499).

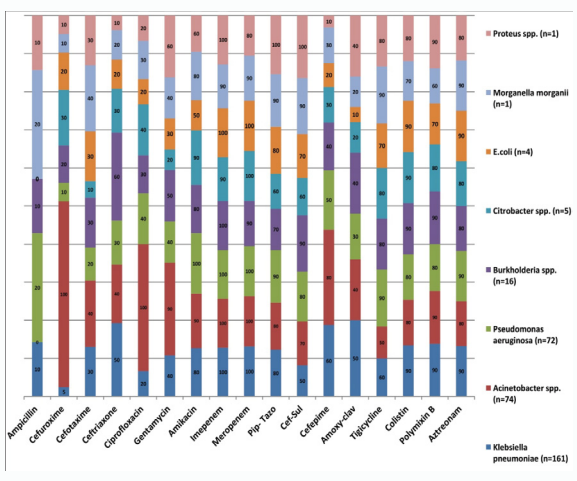

Figure 2: Antibiotic Sensitivity Pattern of Gram Negative Bacteria (Expressed as Percentage of a Particular Organism to Individual Antibiotic)

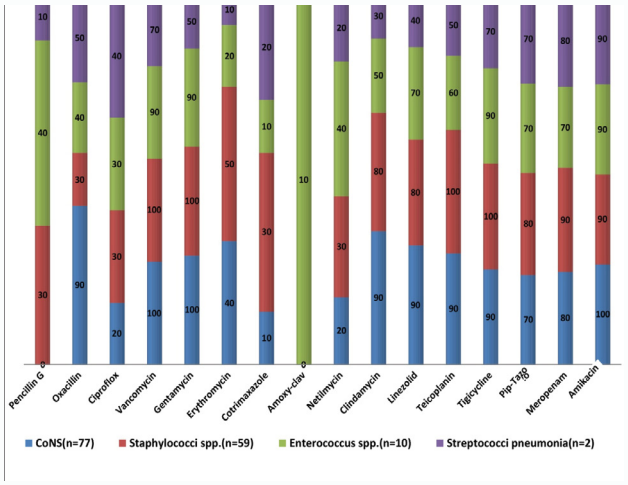

Figure 3: Antibiotic sensitivity pattern of Gram positive bacteria (expressed as percentage of a particular organism to individual antibiotic).

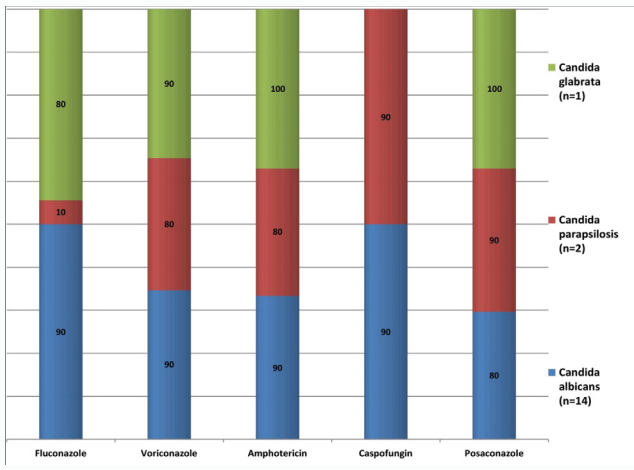

Figure 4: Antifungal sensitivity pattern of different fungi isolated (expressed as percentage of a particular fungi to individual antifungal agent).

In addition to GNBs and GPBs, *Candida* spp. (both *albicans* and *non-albicans*) were also found in the present cohort (Figure 1). *C. albicans* had shown almost similar *in vitro* sensitivity pattern (Figure 4) to all the commonly used antifungal agents. *C. glabrata* and *C. parapsilosis* had shown poor sentivity to caspofungin and fluconazole respectively. In present day hemato-oncology practice, invasive fungal infections becoming increasingly important in critically ill patients. The increased emergence of *non-albicans Candida* spp. as human pathogens are attributed to type of hematological malignancy, prophylactic antifungal therapy and improved identification methods [21].

In FN, after proper risk assessment based on MASCC risk index [22], administration of parenteral broad-spectrum empirical antibiotic therapy in high risk patients is the accepted standard of care [1]. Local antimicrobial trend and drug sensitivity pattern including resistance guides us for choice of empiric therapy. Till recently, antibiotic policy followed at our Institute was to start with Pip-tazo monotherapy and escalate if required based on clinical evaluation of individual patient and the antimicrobial sensitivity report (after it was made available) that is also being followed by most other centers throughout the world as per recommendation by IDSA [1]. And, selective drugs with Gram positive coverage were added when there is suspected focus of infection as mentioned in the guidelines. Study by Ng TM et al. [23] from Singapore, have shown similar efficacy of empiric piperacillin-tazobactam *versus* carbapenems in treatment of *bacteraemia* due to Extended-Spectrum Beta-Lactamase (ESBL)-Producing *Enterobacteriaceae* in a cohort with mainly urinary tract infections. Oztoprak N et al. [24] from Turkey recently published results of an Open Randomized Trial on Piperacillin–tazobactam Versus Carbapenem Therapy With and Without Amikacin as Empirical Treatment of FN; have shown efficacy of empirical therapy with piperacillin-tazobactam is equivalent to carbapenem in adult FN patients. Horita N et al. [25] from Japan systematically reviewed different anti-pseudomonal β-lactams for FN empiric therapy and shown Imipenem/cilastatin, pip-tazo and meropenem to be reasonable first-choice therapy for empiric therapy. However, the present study done with a significant cohort size is an eye opener to us where many strains of GNBs and GPBs are showing increasing resistance to pip-tazo. As well evident in Figure 2 & Figure 3, there is a trend of overall very good sensitivity of both GNBs and GPBs to carbapenems and aminoglycosides (except netilmicin); carbapenems may be used as empirical monotherapy. Aminoglycoside not being used in our center as part of empirical therapy till recently, could be the reason for the preserved sensitivity across the different types of micro-organisms; and that can justify its use in combination with meropenem in selected cases if clinically indicated. Considering resistance to fluconazole in *Candida non-albicans*, we have now adopted voriconazole antifungal prophylaxis as an Institutional policy.

Conclusion

The present study shows the change in trends of micro-organisms with a shift to the prevalence of Gram-negative bacteria. With detection of emerging pathogens such as *Acinetobacter* spp., *Burkholderia* spp. and *Candida non-albicans* with inherent multidrug resistance in increasing proportion is a matter of great concern for the treating physicians in a hemato-oncology care center. Knowledge of the change in trends of micro-organisms isolated in individual hospital and the antimicrobial sensitivity pattern helps the clinicians to overcome multidrug resistance and better patient outcome.

Ethical Consideration

The study conducted prospectively with hospitalized patients; proper informed and written consent taken from the patients and /or their legal guardians, in case of minor and very sick patients. And the study was conducted as per Institutional Ethical Committee protocol.

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Authors Contribution

PKM, VK, AB, TKD- Concept, study design, clinical studies, data collection and analysis, literature search, manuscript preparation, manuscript editing, manuscript review and approval. SB, BD, AS,

MJ, PSS, AB, MG, RD- study design, clinical studies, data collection, manuscript editing, review and approval.

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