



Retrospective Analysis of Blood Stream Infections and Antibiotic Susceptibility Pattern of Gram Negative Bacteria in a Tertiary Care Cancer Hospital

Radha Rani D^{1*}, Sridevi Chaitanya B¹, Senthil Rajappa J², Basanth Kumar R³, Krishna Prabhakar K⁴, Krishna Mohan MVT², Vibhavari Nayak K³, Pavan Kumar², Ayyagari Santa² and T. Subramanyeshwara Rao⁵

¹ Department of Microbiology, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India

² Department of Medical Oncology, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India

³ Department of Anaesthesiology, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India

⁴ Department of Critical Care Medicine, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India

⁵ Department of Surgical Oncology, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India

*Corresponding e-mail: dradharani@gmail.com

ABSTRACT

Background: Bacterial bloodstream infections are important causes of morbidity and mortality globally. The aim of the present study was to determine the bacterial profile of bloodstream infections and their antibiotic susceptibility pattern among the clinically diagnosed cases of sepsis in cancer patients. **Methods:** In the present study, etiological and antimicrobial susceptibility profile of blood cultures over a period of 1 year at a tertiary cancer care hospital was done. Blood culture positive isolates were identified using standard microbiological methods and by Fully automated BD Phoenix 100. The antibiotic susceptibility pattern of the organisms was performed by Kirby-Bauer disc diffusion method and MIC (Minimum inhibitory concentration) was done by Fully automated BD Phoenix 100. **Results:** There were 1178 blood culture samples, of which 327 (27.7%) were identified to be culture positive. Out of 327 positive cultures, 299 (91.4%) showed bacterial growth, Gram negative were 161 (53.8%) and Gram positive were 138 (46.1%). *Candida* species were isolated from 13 (3.97%) of positive samples and 15 samples showed contamination. The most common Gram-negative isolate was *Escherichia coli* (37.80%) and Gram-positive isolate was coagulase-negative staphylococci (52.80%). *Escherichia coli* showed highest sensitivity to amikacin (83.60%) and sensitivity to piperacillin+ tazobactam and cefaperazone+sulbactam was 54.09% and 52.45% respectively. High degree of resistance was found to cephalosporins and levofloxacin. **Conclusion:** The results indicate high level of antimicrobial resistance among Gram negative bacilli in septicemic patients. The results warrant continuous monitoring of antimicrobial pattern so as to build geographical epidemiological data.

Keywords: Blood stream infections (BSI), Antimicrobial susceptibility, Bacteremia, Resistance

INTRODUCTION

Infectious complications consequent to the immunosuppressive therapy has become a major cause of morbidity and mortality in cancer patients [1]. The cancer patient is immunocompromised due to nature of the disease and due to interventions in the form of chemotherapy. Other associated risk factors for acquiring infection are long term catheterization, mucositis due to cytotoxic agents, neutropenia, and stem cell transplantation [2]. Blood stream infections increase the length of hospital stay, cause significant morbidity and mortality and increase the cost of care.

The situation further deteriorates with increasing rate of multidrug resistance. The crude mortality rate due to BSIs in cancer patients ranges from 18% to 42% [3-6]. The organisms and their antibiotic susceptibility pattern varies among different healthcare facilities and geographical areas. Blood culture is the single most reliable procedure for bacterial isolation and detection. The aim of the present study was to determine the bacterial profile of bloodstream infections and to assess the antibiotic susceptibility pattern of the major pathogens among the clinically diagnosed cases of sepsis in cancer patients.

MATERIALS AND METHODS

This was a retrospective study conducted at a tertiary care hospital for cancer patients. We analyzed all blood samples sent for bacterial culture during the year 2016.

A total of 1178 blood samples from clinically diagnosed cases of sepsis, received in the microbiology laboratory of a 450-bedded cancer hospital of south India over duration of one year, were included in the study. Blood samples were collected before the administration of antibiotics. Relevant details of the patients were recorded. Blood culture bottles from Biomerieux were inoculated with the sample and incubated in BACT/ALERT 3D. When the instrument signaled positive, sub cultures were done on blood agar, MacConkey agar and chocolate agar. The growth obtained was identified by colony morphology, Gram stain of the isolated colonies, standard microbiological, biochemical tests and by fully automated BD Phoenix 100.

The antibiotic susceptibility pattern of the isolated organisms was performed by Kirby-Bauer disc diffusion method on Mueller-Hinton agar plates as well as MICs were done by fully automated BD Phoenix 100 and the results were interpreted as per the Clinical and Laboratory Standards Institute (CLSI) 2016 guidelines. Cefoxitin disc diffusion method was used to identify MRSA (Methicillin resistant *Staphylococcus aureus*) as per CLSI guidelines. MDR (Multi drug resistant) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. The antibiotic discs that were used to identify the susceptibility pattern of the gram-negative pathogens and their concentrations include amikacin (30 mcg), amoxicillin+clavulanic acid (20/10 mcg), ceftazidime (30 mcg), ceftriaxone (30 mcg), cefepime (30 mcg), cefoperazone+sulbactam (75/30 mcg), imipenem (10 mcg), meropenem (10 mcg), piperacillin+tazobactam (100/10 mcg), levofloxacin (5 mcg), cotrimoxazole (1.25/23.75).

RESULTS

This study was carried out from January 2016 to December 2016 with 1178 blood samples receive from patients suspected of having bloodstream infections attending and admitted in Basavatarakam Indo-American cancer Hospital, Hyderabad. Details like medical registration number, laboratory number, age and sex of the patients, and type and place of collection of specimen were recorded. Culture positivity was seen in 327 (27.35%) samples, and 851 (72.24%) samples were sterile (Table 1) as detected with the BACT/ALERT 3D (Biomerieux) blood culture system.

Table 1 Ward wise distribution of blood cultures and positivity rate

S. No	Location	Blood cultures received	No Growth (%)	Growth (%)
1	Wards	575	426 (74.08)	149 (25.9)
2	MICU	312	193 (61.8)	119 (38.14)
3	BMT	232	185 (79.74)	47 (20.25)
4	SICU	17	11 (64.7)	06 (35.2)
5	OP	42	36 (85.7)	06 (14.28)
6	TOTAL	1178	851 (72.24)	327 (27.75)

Out of total 1178 samples received, 705 (59.84%) were males and 473 (40.15%) were females. Overall Blood culture positivity rate among males was 16.29% and 10.95% among females (Table 2).

Table 2 Age wise and sex wise distribution (Blood cultures Jan 2016 - Dec 2016)

Age group	Males (705)		Females (473)		Total
	Growth	No growth	Growth	No growth	
<20	28	98	21	65	212
21-40	57	121	29	92	299
41-60	69	179	58	124	430
>60	38	115	27	57	237
Total	192 (16.29%)	513 (43.54%)	135 (10.95%)	338 (29.20%)	1178

Out of 327 positive cultures, 299 (91.4%) showed bacterial growth, Gram-negative were 161 (53.8%) and Gram positive were 138 (46.1%). *Candida* species were isolated from 13 (3.97%) of positive samples and 15 samples showed contamination. Among Gram-negative isolates *Escherichia coli* (37.80%) was found to be most predominant followed by *Klebsiella* species (24.20%), *Pseudomonas* species (13.60%) and *Acinetobacter* species (6.80%) (Figure 1). Among Gram-positive isolates coagulase negative *Staphylococci* (52.80%) was most predominant followed by *Staphylococcus aureus* (14.40%) and *Enterococcus* species (10.14%) (Figure 2).

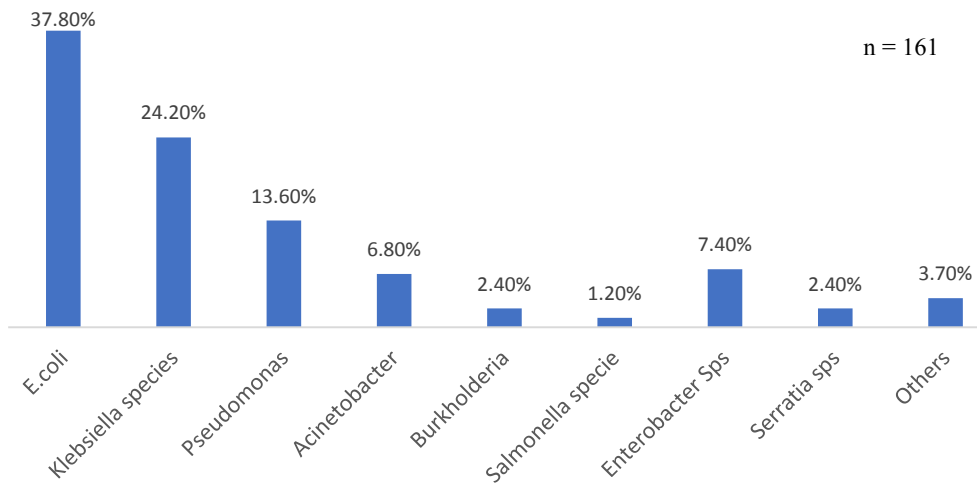


Figure 1 Percentage of gram negative isolates

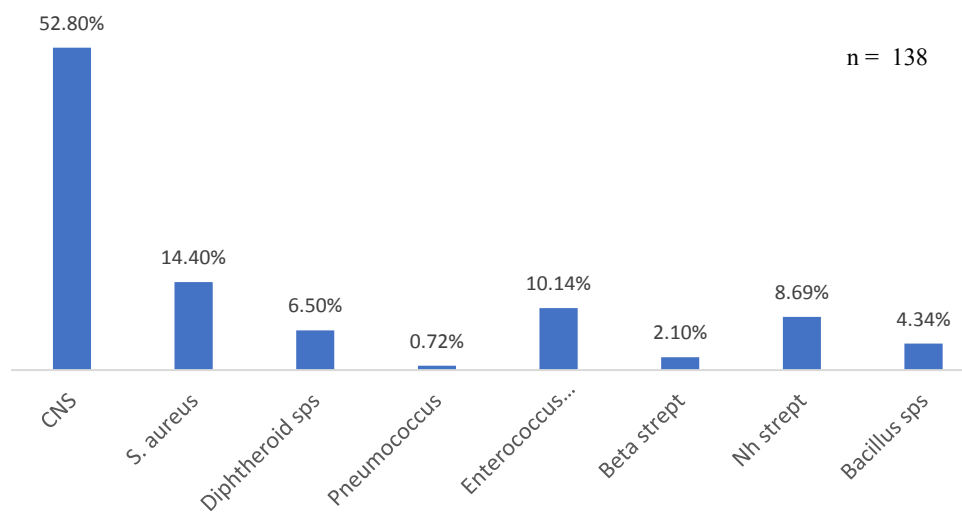


Figure 2 Percentage of gram positive isolates

Antibiotic sensitivity pattern of Gram-negative and Gram-positive organisms was studied. Out of 61 *Escherichia coli* isolates 83.60% were sensitive to amikacin and 67.21% and 65.57% of isolates were sensitive to meropenem and imipenem respectively. Only 13.11% of isolates were sensitive to levofloxacin and 18.03% were sensitive to cefepime showing high degree of resistance to both the drugs (Figure 3).

Klebsiella species showed lower sensitivity to amikacin (61.53%) and a higher sensitivity to levofloxacin (51.28%) and cefepime (25.64%) as compared to *Escherichia coli*. Sensitivity to imipenem and meropenem in *Klebsiella* species was 53.84% and 56.41% respectively (Figure 4). Non-fermenters *Pseudomonas* species and *Acinetobacter* species had a sensitivity of 81.8% and 72.70% to amikacin (Figures 5 and 6). Unlike *Escherichia coli* and *Klebsiella* species the non-fermenters *Pseudomonas* species and *Acinetobacter* species had 77.2% and 81.8% sensitivity to levofloxacin (Figures 5 and 6). Among 61 *Escherichia coli* isolates 80.30% were ESBL (extended spectrum beta lactamase) and 22.90% were MDR and among 39 *Klebsiella* isolates 64.10% were ESBL producers and 41.02% were

MDR. MDR *Pseudomonas* and *Acinetobacter* were in the range of 13.60% and 18.18% respectively. Out of the total 20 *Staphylococcus aureus* isolates 15% were MRSA.

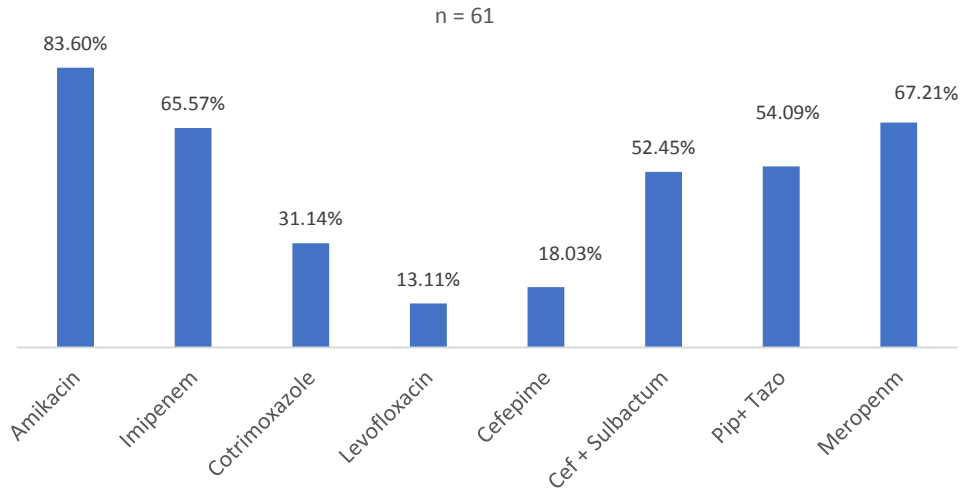


Figure 3 Antibiotic sensitivity pattern of *Escherichia coli* isolates

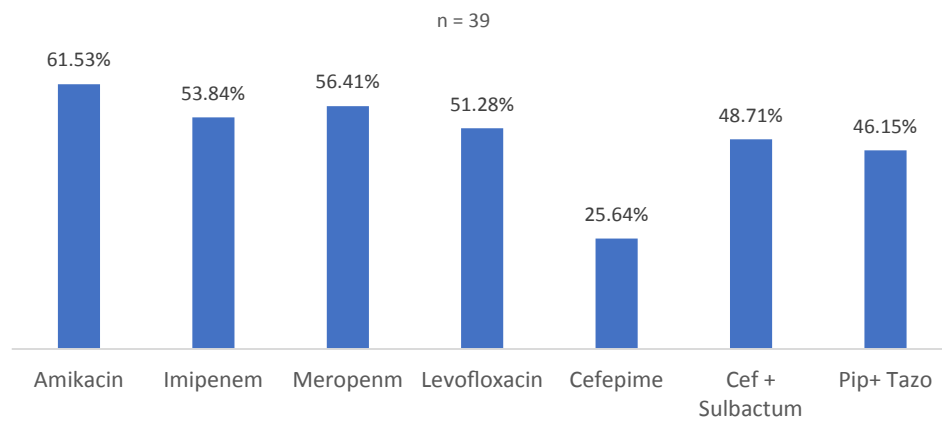


Figure 4 Antibiotic sensitivity pattern of *Klebsiella* isolates

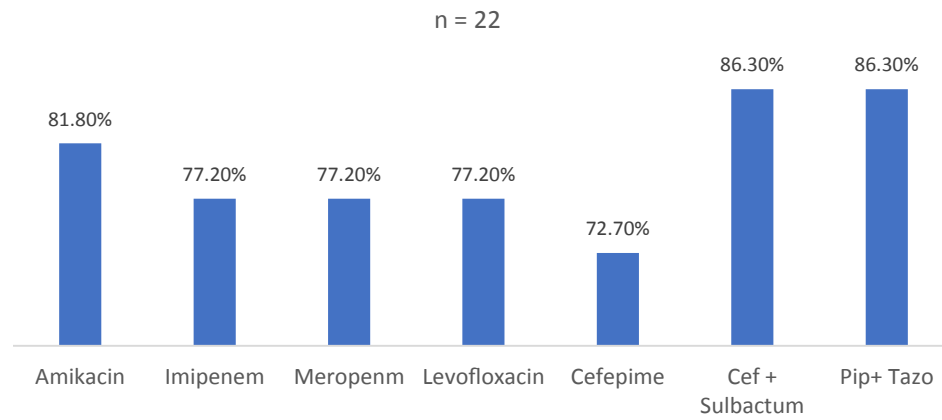


Figure 5 Antibiotic sensitivity pattern of *Pseudomonas* isolates

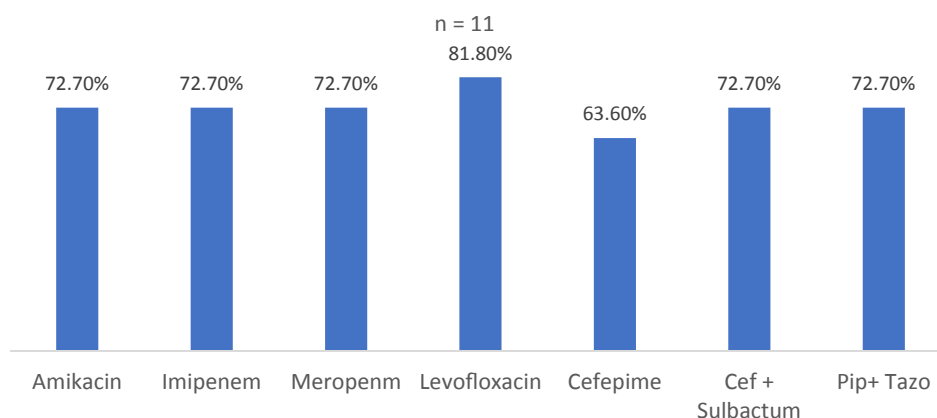


Figure 6 Antibiotic sensitivity pattern of *Acinetobacter* isolates

DISCUSSION

The present study provides information on the distribution of bacterial isolates causing bloodstream infections along with their antibiotic susceptibility pattern that plays a crucial role in effective management of septicemic cases. In our study, the blood culture positivity rate in clinically suspected septicemia cases was 27.35%, which was approximately similar to the studies by Venkatesh, et al. [7] which showed positivity of 27.16%, Wasihun, et al. [8] showed 28%, Ali, et al. [9] showed 24.2%, Nikita Vasudeva, et al. [10] showed 31.2% positivity. This is in contrast to other studies which have shown blood culture positivity rates between 9.94% to 11.2% [11-15]. Such differences in prevalence of BSI could be due to the different methodology used in blood culture system, the study design, geographical location, nature of patient population, epidemiological difference of the etiological agents and differences in the infection control policies [16-18].

In our study, Gram-negative and Gram-positive bacteria constituted 54.76% and 46.90% respectively. This finding was in accordance with other studies [13,19-24] where Gram-negative *bacilli* have taken over the Gram-positive organisms.

In the present study, the predominant Gram-negative isolates were *Escherichia coli* (37.8%), followed by *Klebsiella* species (24.2%), *Pseudomonas* species (13.6%) and *Acinetobacter* species (6.8%) which was in concordance with other studies [25-29]. In contrast to this finding, a study from Mumbai revealed that, *Pseudomonas* species was the most common cause (30.37%) and *Escherichia coli* and *Klebsiella* species accounted to 16.06% and 10.61% respectively [23].

In a recent study from Lebanon, *Escherichia coli* represented 39.5% of all Gram-negative organisms [25]. In another study from Pakistan to evaluate drug resistance amongst bacteremic isolates of febrile neutropenic patients, *Escherichia coli* was found to be the most predominant organism of the *Enterobacteriaceae* group while *P. aeruginosa* and *Acinetobacter* species were the most common isolates among the non-*Enterobacteriaceae* group [26].

In our study the predominant Gram-positive isolate was coagulase-negative *Staphylococci* (52.80%) followed by *Staphylococcus aureus* (14.40%) and *Enterococcus* species (10.14%). This finding is similar to other studies where coagulase-negative *Staphylococci* has contributed to blood stream infections in cancer patients [28,30,31]. Some authors have demonstrated that coagulase-negative *Staphylococcus* adheres to the catheter surface, and produces slime, which are risk factors for BSI [32]. This is in contrast to other studies where *Staphylococcus aureus* was the most common isolate [23,33,34].

The prevalence of ESBL producers among *Escherichia coli* and *Klebsiella* species was 80.30% and 64.10% in the present study which is higher than a study from Delhi published in 2010 where 70.7% of *Klebsiella* isolates and 41.7% of *Escherichia coli* isolates were ESBL producers [35]. This is somewhat similar to a study from Saudi Arabia where 79% of all *Escherichia coli* and *K. pneumoniae* isolated were ESBL (extended-spectrum β -lactamases) producing [36]. Hospitalization in the previous 3 months and co morbidity could be the risk factors associated with infections by the ESBL-producing Gram-negative bacteria [37]. Patients at high risk for developing colonization or infection

with ESBL-producing organisms are often seriously ill patients with prolonged hospital stays and in whom invasive medical devices are present (urinary catheters, endotracheal tubes, central venous lines) for a prolonged duration. Heavy antibiotic use is also a risk factor for acquisition of an ESBL-producing organism [38]. The high isolation rates of ESBL producers in our hospital could be because our hospital being a cancer hospital most of our patients require repeated hospitalization, also have invasive devices and are often seriously ill patients who require prolonged hospital stays.

Among *Escherichia coli* and *Klebsiella* species Imipenem sensitivity was seen in 65.57% and 53.84% respectively. All showed 100% susceptibility to colistin. Sensitivity to β -lactam/ β -lactamase inhibitors (piperacillin+tazobactam, cefoperazone+sulbactam) among *Escherichia coli* was 54% and 53% and among *Klebsiella* species was 46% and 49% respectively. This is similar to a study from Mumbai where susceptibility to carbapenems was 70% and, β -lactam/ β -lactam inhibitors (piperacillin+tazobactam, cefoperazone+sulbactam) were 56.5% [39]. Both *Escherichia coli* and *Klebsiella* showed highest activity to amikacin, 83.60% and 61.53% respectively. This high resistance to carbapenems could be because majority of the patients reported to us are referred by other specialists or hospitals and these patients were offered antibiotics elsewhere before they reached our hospital. With this observation on emergence of carbapenem-resistant *Enterobacteriaceae* it is important to give due attention to infection control and antibiotic stewardship.

A high degree of resistance to cephalosporins among *Enterobacteriaceae* in the present study could be due to the fact that cephalosporins are one of the most commonly used antibiotics for inpatients as well as for outpatients in developing countries and other reason is that in most of the cases self-medication is very common as the medicines are available at the counter [40].

Among non-fermenters, *Pseudomonas* showed highest sensitivity to β -lactam/ β -lactam inhibitors and amikacin and *Acinetobacter* species showed highest sensitivity to levofloxacin and amikacin. Sensitivity to Imipenem was 77% in *Pseudomonas* species and 73% in *Acinetobacter* species. All our isolates were sensitive to colistin. This is in contrast to a study from Mumbai where imipenem sensitivity was (91.82%) followed by piperacillin+tazobactam sensitivity (67.27%) and amikacin sensitivity was (50%). Colistin showed (94.55%) sensitivity [22]. The high resistance rate of non-fermenters to imipenem in the present study is of concern.

CONCLUSION

This study provides information on antibiotic resistance of blood isolates which may be a useful guide for physicians initiating empiric therapy. The high prevalence of antimicrobial resistance in Gram-negative isolates is alarming. Routine surveillance of baseline resistance, formulation of hospital antibiotic policy and compliance with existing guidelines will go long way in reducing drug resistance in pathogens. Specific antibiotic utilization strategies like antibiotic restriction, combination therapy and usage according to the standard antimicrobial susceptibility testing may help to decrease or prevent the emergence of resistance.

DECLARATIONS

Conflict of Interest

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

REFERENCES

- [1] Nucci, Marcio, et al. "Risk factors for death among cancer patients with fungemia." *Clinical Infectious Diseases* Vol. 27, No. 1, 1998, pp. 107-11.
- [2] Bhat, Vivek, et al. "Bacteriological profile and antibiotic susceptibility patterns of clinical isolates in a tertiary care cancer center." *Indian Journal of Medical and Paediatric Oncology: Official Journal of Indian Society of Medical & Paediatric Oncology* Vol. 37, No. 1, 2016, p. 20.
- [3] Collin, Berjan A., et al. "Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients." *Clinical Infectious Diseases* Vol. 33, No. 7, 2001, pp. 947-53.
- [4] Krupova, I., et al. "Bacteremia and fungemia in pediatric versus adult cancer patients after chemotherapy: comparison of etiology, risk factors and outcome." *Journal of Chemotherapy* Vol. 10, No. 3, 1998, pp. 236-42.

- [5] Krcmery, V., et al. "Bacteremia due to multiresistant gram-negative bacilli in neutropenic cancer patients: a case controlled study." *Journal of Chemotherapy* Vol. 10, No. 4, 1998, pp. 320-25.
- [6] Ehni, William F., L. Barth Reller, and Richard T. Ellison III. "Bacteremia in granulocytopenic patients in a tertiary-care general hospital." *Reviews of Infectious Diseases* Vol. 13, No. 4, 1991, pp. 613-19.
- [7] Venkatesh, V., and Swapna Kotian. "Bacteriological profile and antimicrobial resistance of blood culture isolates among paediatric patients from tertiary care hospital." *Journal of International Medicine and Dentistry* Vol. 3, No. 2, 2016, pp. 80-87.
- [8] Wasihun, Araya Gebreyesus, et al. "Bacteriological profile and antimicrobial susceptibility patterns of blood culture isolates among febrile patients in Mekelle Hospital, Northern Ethiopia." *SpringerPlus* Vol. 4, No. 1, 2015, p. 314.
- [9] Ali, J., and Y. Kebede. "Frequency of isolation and antimicrobial susceptibility pattern of bacterial isolates from blood culture, Gondar University teaching hospital, Northwest Ethiopia." *Ethiopian Medical Journal* Vol. 46, No. 2, 2008, pp. 155-61.
- [10] Vasudeva, Nikita, Prem Singh Nirwan, and Preeti Shrivastava. "Bloodstream infections and antimicrobial sensitivity patterns in a tertiary care hospital of India." *Therapeutic Advances in Infectious Disease* Vol. 3, No. 5, 2016, pp. 119-27.
- [11] Mehta, Manjula, Priya Dutta, and Varsha Gupta. "Antimicrobial susceptibility pattern of blood isolates from a teaching hospital in North India." *Japanese Journal of Infectious Diseases* Vol. 58, No. 3, 2005, p. 174.
- [12] Arora, Usha, and Pushpa Devi. "Bacterial profile of blood stream infections and antibiotic resistance pattern of isolates." *JK Science* Vol. 9, No. 4, 2007, pp. 186-90.
- [13] Mehta, Manjula, Priya Dutta, and Varsha Gupta. "Antimicrobial susceptibility pattern of blood isolates from a teaching hospital in North India." *Japanese Journal of Infectious Diseases* Vol. 58, No. 3, 2005, p. 174.
- [14] Shalini S, Kranthi K, Gopalkrishna BK. "The microbiological profile of nosocomial infections in the intensive care unit." *Journal of Clinical and Diagnostic Research* Vol. 4, 2010, pp. 3109-12.
- [15] Ghadiri, Hamed, et al. "The antibiotic resistance profiles of bacterial strains isolated from patients with hospital-acquired bloodstream and urinary tract infections." *Critical Care Research and Practice* 2012, 2012.
- [16] Gohel, Kalpesh, et al. "Bacteriological profile and drug resistance patterns of blood culture isolates in a tertiary care nephrourology teaching institute." *BioMed Research International* 2014, 2014.
- [17] Zenebe, Tizazu, et al. "Invasive bacterial pathogens and their antibiotic susceptibility patterns in Jimma University specialized hospital, Jimma, Southwest Ethiopia." *Ethiopian Journal of Health Sciences* Vol. 21, No. 1, 2011, pp. 1-8.
- [18] Dagnew, Mulat, et al. "Bacterial profile and antimicrobial susceptibility pattern in septicemia suspected patients attending Gondar University Hospital, Northwest Ethiopia." *BMC Research Notes* Vol. 6, 2013.
- [19] Vanitha, Rani N., et al. "A retrospective study on blood stream infections and antibiotic susceptibility patterns in a tertiary care teaching hospital." *International Journal of Pharmacy and Pharmaceutical Sciences* Vol. 4, No. 1, 2012, pp. 543-48.
- [20] Gupta, Shilpi, and Bineeta Kashyap. "Bacteriological profile and antibiogram of blood culture isolates from a tertiary care hospital of North India." *Tropical Journal of Medical Research* Vol. 19, No. 2, 2016, p. 94.
- [21] Pal, Nidhi, and RaMaMuRthy Sujatha. "Antimicrobial resistant pattern of blood culture isolates, among septicemia suspected patients." *National Journal of Laboratory Medicine* Vol 5, No. 1, 2016, pp. 17-21.
- [22] Sonawane, Jyoti P., et al. "Bacteriological profile and antimicrobial susceptibility of blood culture isolates from tertiary care hospital, Navi Mumbai." *Journal of Medical Science and Clinical Research* Vol. 5, No. 1, 2016, pp. 17-21.
- [23] Prabhash, Kumar, et al. "Blood stream infections in cancer patients: A single center experience of isolates and sensitivity pattern." *Indian Journal of Cancer* Vol. 47, No. 2, 2010, p. 184.
- [24] Chen, Chien-Yuan, et al. "Trends and antimicrobial resistance of pathogens causing bloodstream infections among febrile neutropenic adults with hematological malignancy." *Journal of the Formosan Medical Association* Vol.

- 103, No. 7, 2004, pp. 526-32.
- [25] Moghnieh, Rima, et al. "Third generation cephalosporin resistant Enterobacteriaceae and multidrug resistant gram-negative bacteria causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis." *Frontiers in Cellular and Infection Microbiology* Vol. 5, 2015.
- [26] Irfan, Seema, et al. "Emergence of Carbapenem resistant Gram negative and vancomycin resistant Gram-positive organisms in bacteremic isolates of febrile neutropenic patients: a descriptive study." *BMC Infectious Diseases* Vol. 8, No. 1, 2008, p. 80.
- [27] Al-Otaibi, Fawzia E., et al. "Prevalence and risk factors of Gram-negative bacilli causing blood stream infection in patients with malignancy." *Saudi Medical Journal* Vol. 37, No. 9, 2016, p. 979.
- [28] Gustinetti, Giulia, and Malgorzata Mikulska. "Bloodstream infections in neutropenic cancer patients: a practical update." *Virulence* Vol. 7, No. 3, 2016, pp. 280-97.
- [29] Bansal, S, and SH Advani. "Pattern of bloodstream infections in patients with hematological malignancies in a tertiary care centre." *Indian Journal of Cancer* Vol. 51, No. 4, 2014, pp. 447-449.
- [30] Ahmed, N.H., F.K. Baruah, and R.K. Grover. "Letter to Editor: Staphylococcal Blood Stream Infections in Cancer Patients." *Annals of Medical and Health Sciences Research* Vol. 5, No. 3, 2015, pp. 226-27.
- [31] Velasco, Eduardo, et al. "Epidemiology of bloodstream infections at a cancer center." *Sao Paulo Medical Journal* Vol. 118, No. 5, 2000, pp. 131-38.
- [32] Raad, I., et al. "Serious complications of vascular catheter-related *Staphylococcus aureus* bacteremia in cancer patients." *European Journal of Clinical Microbiology & Infectious Diseases* Vol. 11.8 (1992): 675-682.
- [33] Babu, K. Govind, 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* Vol. 37, No. 3, 2016, p. 174.
- [34] Kang, Cheol-In, et al. "Bloodstream infections in adult patients with cancer: clinical features and pathogenic significance of *Staphylococcus aureus* bacteremia." *Supportive Care in Cancer* Vol. 20, No. 10, 2012, pp. 2371-78.
- [35] Taneja, Juhi, et al. "Nosocomial blood-stream infections from extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumonia* from GB Pant Hospital, New Delhi." *The Journal of Infection in Developing Countries* Vol. 4, No. 08, 2010, pp. 517-20.
- [36] Mustafa, Sabir Awad. "High Prevalence and Antibiogram Pattern of Extended Spectrum Beta Lactamases Producing *Escherichia Coli* and *Klebsiella Pneumonia* Isolated from Inpatients Units in a General Hospital in Saudi Arabia." *EC Microbiology* Vol. 5, 2017, pp. 30-35.
- [37] Gedik, H. "Does antimicrobial use increase the rate of antimicrobial resistance: A one year experience." *Indian Journal of Medical Microbiology* Vol. 30, 2012, pp. 198-202.
- [38] Rawat, Deepti, and Deepthi Nair. "Extended-spectrum β -lactamases in gram negative bacteria." *Journal of Global Infectious Diseases* Vol. 2, No. 3, 2010, p. 263.
- [39] Singhal, T., S. Shah, and R. Naik. "The microbial etiology and antimicrobial susceptibility of bloodstream infections in patients with cancer at a private tertiary care hospital in Mumbai, India." *Indian Journal of Cancer* Vol. 53, No. 3, 2016, p. 452.
- [40] Nathisuwan, Surakit, David S. Burgess, and James S. Lewis. "Extended-spectrum β -lactamases: epidemiology, detection, and treatment." *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* Vol. 21, No. 8, 2001, pp. 920-28.