Research Paper

INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH
ISSN: O: 2319-6475, ISSN: P: 2319-6505
Available Online at www.journalijcar.org
Volume 14; Issue 04; April 2025; Page No.143-147
DOI: http://dx.doi.org/10.24327/ijcar.2025.147.0033

Subject Area : Anaesthesia

BACTERIOLOGICAL PROFILE AND ANTIBIOTIC SUSCEPTIBILITY OF CLINICAL ISOLATES FROM CANCER PATIENTS WITH FEBRILE NEUTROPENIA ATTENDING A TERTIARY CARE HOSPITAL IN CENTRAL INDIA – A CROSS-SECTIONAL STUDY

Dr. Krishna Lekha T[1], Dr. Sonal Chavan[2], Dr. Sunanda Shrikhande (Zodpey)[3]

[1]Junior Resident, [2]Associate professor, [3]Professor and Head of the Department

Department of Microbiology, G.M.C. Nagpur

Article History: Received 11th March 2024., Received in revised form 20th March, 2024., Accepted 13th April, 2025.,Published online 28th April, 2025

Key words: Febrile neutropenia (FN)) Blood stream infection (BSI), Methicillin-resistant *Staphylococcus aureus* (MRSA), MR CoNS (Methicillin resistant Coagulase negative *Staphylococci)*

INTRODUCTION

Cancer is the major cause of morbidity and mortality in the modern world, probably because the disease is diagnosed in the advanced stages. And it is one of the major public health problems causing high mortality. According to a recent study, India registered 9.3 lakhs of cancer deaths in the year 2019, which is the second largest in Asia.[1] The outcome of the disease, depends on the type of cancer, stage of diagnosis. Chemotherapeutic regimen using, occurrence of infection and immune response of the patients. One type of blood elements whose number commonly decreases during cancer is the group of neutrophils, which constitutes the first line of the body defence against diseases. Neutropenic fever is the most common and serious complication associated with hematopoietic cancers or with patients receiving chemotherapeutic regimens for cancer. The host barriers such as the mucosal lining of the GI tract or sinuses, may be damaged, leading the host open to invasion from an infectious pathogen. FN can be defined as a single oral temperature≥38.3°Cor101°F or a temperature of ≥ 38°C or 100.4°F for at least 1 hour, With absoluteneutrophil count (ANC) < 500 cells/mm^3 or an ANC < 1,000 cells/mm^3 with apredicteddeclineto<500cells/mm^2[2]

Morbidity and mortality due to cancer may be due to several factors. Febrile neutropenia plays a major role in this. Considering febrile neutropenia as an oncological emergency a proper management plan has to made for the assessing the risk factors and developing an institutional empirical antibiotic policy for the treatment.The management of febrile neutropenia is intravenous empirical antibiotic therapy with symptomatic management.The occurrence of febrile neutropenia will affect the treatment protocol negatively as it will cause treatment discontinuation, delay in the dose, dose reduction, which ultimately lead to prolonged hospital stay and disease burden. With this background in mind, we decided to conduct a study to analyse the bacteriological profile and antibiotic susceptibility of clinical isolates from cancer patients with febrile neutropenia in our institute.

*Corresponding author: **Dr Pradnya Jagtap**

B2 Uday Mitra Soc Kurla East Mumbai, Postal Code 400024 - India

MATERIALS AND METHODS

It is a cross-sectional study conducted in the Department of Microbiology and Department of Onco-radiology over a period of 2 years (from July 2022 to July 2024). Institutional ethics committee approval been taken. Informed consent been taken from each patient participating in this study. Important details regarding illness were collected using the clinical proforma from 200 cancer patient, with Inclusion criteria -males and females of both adult and pediatric age group with clinically diagnosed malignancy presenting with febrile neutropenia, patient with temperature >38˚C for over 1 hour, patients with neutrophil count < 500 cells/mm3.Patients having fever due to non-infectious cause like blood transfusion reaction, drug infusion and Patient who are not willing to be a part of this studywere excluded from this study.

All samples were processed using standard microbiological technique [3]and anti-biotic susceptibility was done by Kirby-Bauer Disk diffusion technique according to CLSI 2022 guidelines.[4] Extended spectrum Beta- lactamase (ESBL) production detection done by Double disk synergy test (DDS). A disk containing BL is placed next to a clavulanate contain-

ing disk (Amoxicillin-clavulanate) with an average gap of 20 mm center to center. Three patterns of findings are interpreted as ESBL positive - Augmentation of the zone of inhibition of BL on the side of clavulanate disk, Appearance of a keyhole in the direction of clavulanate disk or Phantom zone appearance in-between two disks. For Amp C detection Cefoxitin screen test was done. Cefoxitin zone cut-off < 18mm using 30 mg disk with Phenotypic resistance to ceftazidime/cefotaxime (using clinical break points and confirmed by disk antagonism test. For testing Vancomycin sensitivity by MIC (Minimum Inhibitory Concentration) test for MRSA/MRCoNS E- strip of Vancomycin (0.016µg/ml – 256 µg/m concentration -Himedia laboratories) used. MIC value was read where the edge of inhibition ellipse mean intersected the strip.**[Fig.1]**

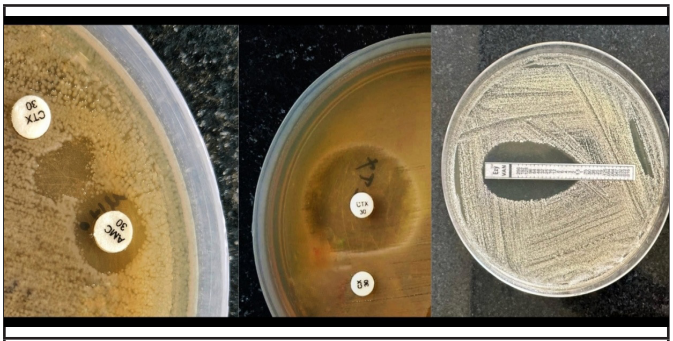

Fig.1 ESBL detection by DDS , Amp C confirmation test, Vancomycin MIC by E -strip

RESULTS

Out of 200 patients, 108 patients were culture positive. Out of 108 patients, 62 (56%) patients were males and 46 (43%) were females. It is showing a male predominance of 56%. Most of the patients were belong to the age group 41-50 years (30%) followed by 31-40 years (24%). Least common age groups affected were 11-20 years and 71-80 years (2% each). Most predominent malignancy causing febrile neutropenia was haematological malignanacy (70%) followed by solid malignancy (30%).Among haematological malignancy, **[Table no.1]**Acute myeloid Leukaemia is the most predominant malignancy accounts for 28% followed by Hodgkin's lymphoma accounts for 17%. The least common malignancy reported causing febrile neutropenia in cancer patients was Pro-myelocytic leukaemia. Most common solid malignancy causing febrile neutropenia according to this study is Head and neck malignancy (11%) followed by bone malignancy (9%). Febrile neutropenia was least reported in gynaecological, urogenital and gastro-intestinalmalignancies (2% each). Blood stream infections and urinary tract infections were the most common infections in cancer patients with febrile neutropenia (35% each). Respiratory tract infections was the second most common infection (28%) reported. Gastro intestinal infection was the least common infection (2%) reported

Table 1. Distribution of haematological malignancy among cancer patients with febrile neutropenia (n=108)

Type of Malignancy	No. of patients (%)
Acute myeloid leukaemia (AML)	30(28%)
Acute Lymphocytic Leukaemia (ALL)	6(6%)
Pro-myelocytic Leukaemia (PML)	2(2%)
Chronic Myeloid Leukaemia (CML)	4(4%)
Hodgkin's lymphoma (HL)	18(17%)
Non-Hodgkin's lymphoma (NHL)	12(11%)
Multiple myeloma (MM)	4(4%)

Out of 108 culture positive cases, 69% of isolates were gram-negative organisms and 31% of them were gram-positive organisms. **Fig. 2. Showing** distribution of gram-positive and gram-negative isolates from various clinical specimens. The most common gram-positive organism isolated in our study was *Staphylococcus aureus* (18%), followed by Coagulase negative *Staphylococci* (7%), mostly isolated from blood sample. Most common gram-negative isolates in our study were*Klebsiella pneumoniae* (30%), followed by *E. coli* (18%), mostly isolated from urine sample. In present study 9% of infections are caused by *Pseudomonas aeruginosa*. The least common gram-negative isolates were *A. baumannii* and *A. lwoffii* (5% and 4% each

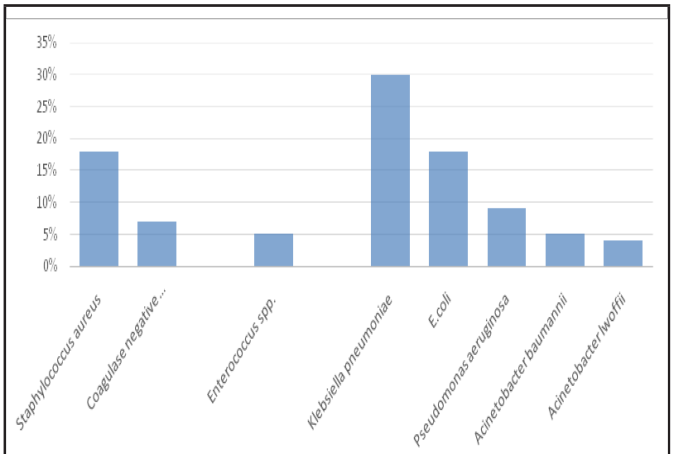

Fig. 2 Distribution of gram-positive and gram-negative organism isolated from clinical specimens from cancer patients with febrile neutropenia (n=108)

In the present study, among gram positive organisms, *Staphylococcus aureus*isolates were showing a lowsensitivity to CX, E and CD (50%, 60% and 60% respectively) and high sensitivity to DO, LZ, GEN and LE (80%,90%, 70% and 80% respectively). Among Coagulase negative Staphylococci all isolates are showing low sensitivity to CX, E, CD, GEN (63%, 50%,50%, 50% respectively) and high sensitivity to LZ and LE (75% each). Vancomycin MIC detected using E-strip for all methicillin resistant strain, all found to be sensitive. All the *Enterococcus* isolates were less sensitive to P, AMP and E (33.3%,66.6% and 50% respectively) and high sensitivity to LZ, VA and TEI (100%, 100% and 83.3% respectively). There was no vancomycin resistant *Enterococci* (VRE) and all isolates of *Enterococcus* were showing 100% sensitivity to TEI and LZ.

Table. 2 showing the sensitivity of gram-negative isolates. All *Enterobacterales* isolates were multi-drug resistant in our study. *K. pneumoniae* isolates were showing low sensitivity to AMP, CZ, CXM, CX, CTX, AMC AND NX (for urinary

isolates). All *E. coli* isolates showing low sensitivity to AMP, CZ, CXM, CX, CTX, AMC AND NX (for urinary isolates). *Pseudomonas aeruginosa*, all were resistant to CAZ. And all of them were showing low sensitivity to PIT, MRP, AT, GEN and TOB. *Acinetobacter* isolates were showing low sensitivity to CAZ, CTX, AMS, PIT, MRP, GEN, TOB. All *Pseudomonas* isolates were resistant to CAZ. And all of them were showing low sensitivity to PIT, MRP, AT, GEN and TOB. *Acinetobacter* isolates were showing low sensitivity to CAZ, CTX, AMS, PIT, MRP, GEN, TOB.

Our 50% *Staphylococcus aureus* and 63% of CoNS were methicillin resistant. Vancomycin MIC was done by E-strip method, for all MRSA and MR CoNS all isolates came sensitive to Vancomycin. ESBL (Extended spectrum beta-lactamase) production among *Enterobacterales*isolates. Among all *Enterobacterales* isolates40.7% of them were ESBL (Extended spectrum beta-lactamase) producers. Majority of them were*Klebsiella pneumoniae* (29.6%) and 11.1% of them were *E. coli*. **[Table. 3]**

Table. 3 ESBL production and Amp C production among gram-negative isolates

Resistance mechanism	Isolates	Number of isolates
ESBL production	*Klebsiella pneumoniae*	16 (29.6%)
	E. coli	6(11.1%)
Amp C production	*Klebsiella pneumoniae*	6 (8%)
	E. coli	4 (5%)

DISCUSSION

In present study febrile neutropenia is showing a male predominance of 56%. In accordance with our findings in a study by Norohna V et al [5], 65.2% of study population were male. The gender of affected patient does not interfere in the results obtained, since febrile neutropenia affects both men and women.[6] The mean age group affected in our study was 41±10 years. In a study by Joudeh N et al [7], the mean age group of affected population was 42.2± 16 years in accordance with our study. According to our finding, FN is common in haematological malignancy (70%). In a study by Lubwama M et al[8] 74% cases were associated with haematological malignancy and 26% of cases of FN cases were reported in solid malignancy. In contradiction to our findings, in a study

Table 2. Antibiotic sensitivity of gram-negative isolates

	Enterobacterales		Non-fermenters		
Drugs	*K. pneumoniae* (n=34)	*E. coli* (n=20)	*P. aeruginosa* (n=10)	*A.baumannii*(n=6)	*A.lwoffii* (n=4)
Ampicillin (AMP)	-	6 (30%)	-	-	-
Cefazolin (CZ)	13 (38.2%)	8 (40%)	-	-	-
Cefuroxime (CXM)	11 (32.4%)	10(50%)	-	-	-
Ceftazidime (CAZ)	-	-	0 (0%)	1 (16.6%)	0 (0%)
Cefotaxime (CTX)	16 (47.1%)	11 (55%)	-	1 (16.6%)	0
Cefoxitin (CX)	14 (41.2%)	10 (50%)			
Cefepime (CPM)	25 (73.5%)	16 (80%)	9 (90%)	5 (83.3%)	0 (0%)
Amoxicillin-clavulanate (AMC)	13 (32.2%)	10 (50%)	-	-	-
Ampicillin-sulbactam (AMS)	-	-	-	2 (33.3%)	0 (0%)
Piperacillin- tazobactam (PIT)	25 (73.5%)	16 (80%)	6 (60%)	3 (50%)	2 (50%)
Aztreonam (AT)	-	-	6 (60%)	-	-
Meropenem (MRP)	29 (85%)	16(80%)	5 (50%)	4 (66.6%)	2 (50%)
Gentamycin (GEN)	22 (64.7%)	13 (65%)	6 (60%)	2 (33.3%)	2 (50%)
Tobramycin (TOB)	22 (64.7%)	13 (65%)	6 (60%)	4 (66.6%)	2 (50%)
Amikacin (AK)	-	4 (66.6%)	3 (75%)	5 (83.3%)	4 (100%)
Minocycline(MI)	-	-	-	4 (66.6%)	3 (75%)
Levofloxacin (LE)	24 (76.5%)	15 (75%)	10 (100%)	5 (83.3%)	3 (75%)
Urinary					
Norfloxacin (NX)	7 (43.8%)	9 (56.3%)	-	-	-
Nitrofurantoin (NIT)	10 (62.55)	12 (75%)	-	-	-
Fosfomycin (FO)	-	12 (75%)	-	-	-

by Bhat S et al [9], 60% of malignancies causing febrile neutropenia in cancer patients were solid malignancy and 40% cases were haematological malignancy. Over all burden of haematological malignancy is higher than solid malignancy, so incidence of febrile neutropenia is also higher with haematological malignancy. Compared to patients receiving chemotherapy for solid tumours, those receiving cytotoxic chemotherapy for haematological malignancies can have prolonged neutropenia for14 days or more, which may increase the chance of infections.[10]Most common haematological malignancy causing FN in present study was Acute myeloid leukaemia (28%), followed by Hodgkin's lymphoma (17%). Similar findings can be seen in a study by Kokkayil P et al [11] occurrence of febrile neutropenia episodes was common in the following order - acute myeloid leukaemia (47%), acute lymphoid leukaemia (17%) and non-Hodgkin's lymphoma (15%), Hodgkin's lymphoma (9%) and others (11%).In present study the most common infection encountered in febrile neutropenia cases was Blood stream infection, urinary tract infection (35% each), followed by respiratory tract infection (28%). Almost similar findings seen in study by Prathyusha Y [12]in 2016, the most common infections in febrile neutropenia cases were blood stream infections (40.8%) and urinary tract infections (22.4%).Blood stream infection in cancer patients with febrile neutropenia is due to frequent contact with health care facilities, use of vascular access devices for chemotherapy and irrational use of antibiotic for empirical treatment.[13]

According to our finding, Gram-negative bacterial infection is common (69%) in FN patients- *K. pneumoniae*(30%)as predominantfollowed by *E. coli*(18%).Most of our gram-negative organisms are isolated from urine, the most common gram-negative organisms causing urinary tract infection are *E. coli* and *Klebsiella pneumoniae.*[14]BSI due to *Staphylococcus aureus* and Coagulase-negative *Staphylococci* infection due to the use of intravascular devices and many invasive procedures. [15]

In current study among *Staphylococcus aureus,* 50% of them are MRSA (*Methicillin-resistant Staphylococcus aureus*). According to Amrita Talukdar et al [16],50% of *Staphylococcus aureus*isolates were resistant to Methicillin. The nasal carriage is an important factor in the epidemiology of MRSA infection and the colonization persist for a very long time and it can easily cause infection, especially in immunocompromised individual. In our study, 63% of the isolates were MR CoNS(Methicillin-resistant Coagulase negative *Staphylococci*). In a study by Choudhari S et al [17], 60% of the isolates of CoNS were MR CoNS showing almost similar findings with our study. Methicillin resistance in CoNS has the capacity to spread resistance mechanisms to other bacteria and found on the skin as a commensal. Because of parenteral feeding, intravascular device drug administration, the incidence of MR CoNS is increasing. Vancomycin sensitivity done in methicillin resistant strains by E strip methods, all strains found to be sensitive. Vancomycin is considered to be an excellent drug for treatment of Methicillin resistant *Staphylococci* for many years and lipoglycopeptides class drugs show excellent in vitro potency. [18]

Among all *Enterobacterales* isolates40.7% of them are ESBL (Extended spectrum beta-lactamase) producers. Majority of them are *Klebsiella pneumoniae* (29.6%) and 11.1% of them were *E. coli.* Altamimi I et al [19] in their study found the predominantESBL producers*were Klebsiella* and *E. coli* (21.7% and 33.4% respectively). Emergence of ESBL producing gram negative bacterial infection is a challenge in developing countries.[20] and common ESBL producers are *Klebsiella* and *E. coli* among all other *Enterobacterales*.[21][22]Among all gram-negative bacterial isolates 13% were Amp C producers. Amp C production is common in *Klebsiella pneumoniae* (8%) followed by *E. coli* (5%). Tekele SG et al[23] found in their study that *K. pneumoniae* and *E. coli* as the principal Amp C producing gram negative bacilli. Among *Enterobacteriaceae* family plasmid mediated Amp C production is common and these genes are horizontally transferred.[24]

CONCLUSION

Febrile neutropenia is one of the common complications in cancer patients, and has to be addressed very seriously as the patients are more prone for various kind of infections during the hospital stay.Isolation of multidrug resistant gram-negative bacteria is a challenge in the treatment of febrile neutropenia in cancer patients. Increase in resistance may be due to the inappropriate use of antibiotics for empirical therapy. Isolation of MRSA and MR CoNS are alarming signs, as nasal colonization is an important epidemiological factor and CoNS being a skin commensal can easily cause infections in immunocompromised individuals like patients with febrile neutropenia. Adhering to strict infections control practices and surveillance can decrease the incidence of infections during hospital stay. In order to decrease the morbidity and mortality due to febrile neutropenia in cancer patients, our study will help to develop an antibiotic policy based on locally prevalent pathogens and their sensitivity pattern.

Acknowledgment

I would like to express my deepsincere gratitude to my guideDr. Sonal Chavan, Associate professor Dr. Sunanda Shrikhande (Zodpey), Professor & Head of Department of Microbiology, G.M.C. Nagpur for fostering supportive working and learning environment. I would like to acknowledge all the staff members of department for their valuable contribution to my study.

References

1. Dorji T, Wangmo S, Dargay S, Dorji N, Dorjey Y, Pradhan B, Pema D, Dema C, Choden J, Dorji T, Mynak ML. Population-level cancer screening and cancer care in Bhutan, 2020–2023: a review. The Lancet Regional Health-Southeast Asia. 2024 May 1;24
2. Davidson S. Principles and practice of Medicine 22nd edition, edited by Nicki R. Coledge, Brian, R walker Stuart. H. Raiston in 7th chapter page.(192).
3. Mackie TJ. Mackie & McCartney practical medical microbiology 14th edition. New York: Churchill Livingstone. 2006,53-425
4. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 32nd ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2022
5. Noronha V, Joshi A, Patil VM, Bhosale B, Muddu VK, Banavali S, Kelkar R, Prabhash K. Pattern of infection, therapy, outcome and risk stratification of patients with febrile neutropenia in a tertiary care oncology

hospital in India. Indian Journal of Cancer. 2014 Oct 1;51(4):470.ncies. The Journal of Infection in Developing Countries. 2018 Jun 30;12(06):442-7.

6. Bezerra, I.C.C., Anominondas, T.C.L., Sisenando, H.A.A.A.C.N., Sisenando, S.T.L.C.N. and Moreira, F.S.M. (2007) Evaluation of Initial Empirical Antimicrobial Therapy in Cancer Patients with Febrile Neutropenia. RevistaInfarma of the Re gional Council of Pharmacy, 19, 114-116
7. Joudeh N, Sawafta E, Abu Taha A, Hamed Allah M, Amer R, Odeh RY, Salameh H, Sabateen A, Aiesh BM, Zyoud SE. Epidemiology and source of infection in cancer patients with febrile neutropenia: an experience from a developing country. BMC Infectious Diseases. 2023 Dec;23(1):1-2.
8. Lubwama M, Phipps W, Najjuka CF, Kajumbula H, Ddungu H, Kambugu JB, Bwanga F. Bacteremia in febrile cancer patients in Uganda. BMC research notes. 2019 Dec;12(1):1-6.
9. Bhat S, Muthunatarajan S, Mulki SS, Archana Bhat K, Kotian KH. Bacterial infection among cancer patients: analysis of isolates and antibiotic sensitivity pattern. International journal of microbiology. 2021;2021(1):8883700
10. Prabhash K, Medhekar A Chizuka A, Suda M, Shibata T, Kusumi E, Hori A, Hamaki T, Kodama Y, Horigome K, Kishi Y, Kobayashi K, Matsumura T. Difference between hematological malignancy and solid tumor research articles published in four major medical journals. Leukemia. 2006 Oct;20(10):1655-7.
11. Kokkayil P, Agarwal R, Mohapatra S, Bakshi S, Das B, Sood S, Dhawan B, Kapil A. Bacterial profile and antibiogram of blood stream infections in febrile neutropenic patients with hematological malignancies. The Journal of Infection in Developing Countries. 2018 Jun 30;12(06):442-7.
12. Prathyusha YH, Vara A, Suguneswari G. Bacteriological profile of clinical isolates in cancer patients with febrile neutropenia in a tertiary care hospital in Kurnool, Andhra Pradesh. Indian J Microbiol Res 2021;8(2):139-141
13. Agrawal SK, Gautam H, Choudhary AH, Das BK, Kumar L, Kapil A. Central line-associated bloodstream infections in cancer patients: An experience from a tertiary care cancer centre. Indian journal of medical microbiology. 2019 Jul 1;37(3):376-80.
14. Pardeshi P. Prevalence of urinary tract infections and current scenario of antibiotic susceptibility pattern of bacteria causing UTI. Indian J Microbiol Res.2018 Jul;5(3):334-8.
15. Singh N, Puri S, Kumar S, Pahuja H, Kalia R, Arora R. Risk factors and outcome analysis of gram-positive bacteremia in critically ill patients. Cureus. 2023 Mar;15(3).
16. Talukdar A, Barman R, Hazarika M, Das G. Bloodstream Infections in Paediatric Cancer Patients with Febrile Neutropenia in a Tertiary Cancer Centre in North-East India. Asian Pacific Journal of Cancer Care. 2023 Oct 21;8(4):691-5.
17. Choudhari S, Gawande R, Watchmaker J, Bamnote P, Mishra P, Dwivedi P. Bloodstream infections in cancer patients in central India: study of pathogens and trend of antimicrobial resistance over five years
18. Holmes NE, Tong SY, Davis JS, Van Hal SJ. Treatment of methicillin-resistant Staphylococcus aureus: vancomycin and beyond. InSeminars in respiratory and critical care medicine 2015 Feb (Vol. 36, No. 01, pp. 017-030). Thieme Medical Publishers
19. Altamimi I, Binkhamis K, Alhumimidi A, Alabdulkarim IM, Almugren A, Alhemsi H, Altamimi A, Almazyed A, Elbih S, Alghunaim R, Altamimi A. Decline in ESBL production and carbapenem resistance in urinary tract infections among key bacterial species during the COVID-19 pandemic. Antibiotics. 2024 Feb 26;13(3):216.
20. Batra U, Goyal P, Jain P, Upadhyay A, Sachdeva N, Agarwal M, Bhurani D, Talwar V, Gupta SK, Doval DC. Epidemiology and resistance pattern of bacterial isolates among cancer patients in a Tertiary Care Oncology Centre in North India. Indian Journal of Cancer. 2016 Jul 1;53(3):448-51
21. Dawra Romika DR, Sinha Mala SM. The prevalence of ESBL among Enterobacteriaceae in a tertiary care hospital of Gujarat, India.
22. Umadevi S, Kandhakumari G, Joseph NM, Kumar S, Easow JM, Stephen S, Singh UK. Prevalence and antimicrobial susceptibility pattern of ESBL producing gram negative bacilli. J Clin Diagn Res. 2011 Apr;5(2):236-9.
23. Tekele SG, Teklu DS, Tullu KD, Birru SK, Legese MH. Extended-spectrum Beta-lactamase and AmpC beta-lactamases producing gram negative bacilli isolated from clinical specimens at International Clinical Laboratories, Addis Ababa, Ethiopia. PLoS One. 2020 Nov 12;15(11):e0241984
24. Jacoby GA. AmpC β-lactamases. Clinical microbiology reviews. 2009 Jan;22(1):161-82.

How to cite this article:

Krishna Lekha T.,Sonal Chavan., Sunanda Shrikhande (Zodpey). (2025) Bacteriological profile and antibiotic susceptibility of clinical isolates from cancer patients with febrile neutropenia attending a tertiary care hospital in central India – A cross-sectional study, International Journal of Current Advanced Research, 14(04), pp.143-147.

****