Prevalence of Enterobacteriaceae in Blood Stream Infections and their Resistance Profile: A Brief Study at a Tertiary Care Hospital

Nosheen Neyazi[1], Fatima Khan[1], Asfia Sultan[1], Anees Akhtar[1]

[1]Department of Microbiology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, UP, India

***Correspondence:**

Nosheen Neyazi,

MBBS Proff. Phase 3, JNMC, AMU Aligarh 202002

neyazi.nosheen@gmail.

ABSTRACT: Introduction: Blood stream infections are the leading complications among the critically ill patients in any hospital setting. Enterobacteriaceae are notoriously involved in the majority of these cases. Also, most of these isolates happen to show resistance to the common drugs available. **Objective:** This study aims to review the drug resistance among *Enterobacteriaceae* family. **Materials and Methods:** Observational analysis of Blood Culture reports obtained from the Microbiology Lab Archives was done for a period of 1 year (Jan 2022-Dec 2022). Blood Culture was performed by BacT/ALERT automated System and Anti

Microbial Susceptibility testing was done by Kirby Bauer Disc Diffusion method as well as VITEK system.**Results:**Out of the 3441 blood culture samples, 505 were positive. There were 155 cases of Gram-Positive bacteria, 114 cases of *Candida* species and 236 cases of Gram-Negative Bacteria. Out of 236, 151 (64%) were members of *Enterobacteriaceae*.99 isolates of *Klebsiella* were reviewed. 92% were resistant to Aminoglycosides, 85% were resistant to one or more Cephalosporins, 84% were resistant to Amoxicillin-Clavulanic acid, 82% were resistant to Carbapenems, 82% were resistant to Tetracyclines, 80% were resistant to Cotrimoxazole, 41% were resistant to Colistin, and 24% were pan drug resistant. **Conclusion:** The choice of antibiotic regimen has become increasingly challenging due to the emergence of Multi Drug Resistant organisms especially *Enterobacteriaceae (Klebsiella, E. coli, Salmonella)*.

Keywords: Enterobacteriaceae, Carbapenems,multi drug resistance

Introduction: Bloodstream infections (BSI) are one of the most destructive but also preventable complications in any Critical health care set-up. It has dramatic consequences ranging from

prolonged hospital stay, additional costs to the patient and the hospital economy as well and nevertheless substantial morbidity as well as mortality. Blood stream infections could be Community acquired (CA-BSI) or Hospital acquired (HA-BSI) [1]Even though the prevalence of CA-BSI is more, patients with HA-BSI are relatively older, are more likely to have co-morbid illnesses and a polymicrobial etiology [2] The problem of BSI's can be attributed to advancement of medical sciences in terms of increased invasive interventions, and therefore they account for 15% of all nosocomial infections and affect approximately 1% of all hospitalized patients[3].About 8.75% cases in Indian ICU's are documented for BSIs.[4] The organisms involved in a Bloodstream infection vary in terms of type of healthcare facility involved, type of catheter use, duration of catheterization, prevalent organisms, immune status of the host, underlying comorbidities of the patient and most importantly the precautions taken for maintaining aseptic conditions while inserting the catheter itself.[5] The current trends point out that among the causative bacteria, *Staphylococcus aureus*, coagulase negative *Staphylococcus* and *Enterococcus faecalis* are the most common Gram-positive organisms. The figure is however dominated by Gram negative organisms mainly of *Enterobacteriaceae* family, and non-fermenters like *Pseudomonas* and *Acinetobacter baumanii*.[6] Among fungi, it is nonalbicans *Candida* species are more common than *Candida albicans*.[7] Because *Enterobacteriaceae* are a common cause of both community acquired and hospital acquired infections, they need to be watched closely [8]. The members of *Enterobacteriaceae* family have evolved through time and have an innate ability to proliferate by developing resistance to several antimicrobials via molecular mechanisms, such as enzyme production, efflux pump overexpression, porin modification, facilitated by plasmid mediated genetic exchanges. [9] Carbapenems were the effective against ESBL and AmpC producing Enterobacteriaceae, but there has been emerging resistant to carbapenem, the last-line antibiotic.[10] According to Centers for Disease Control (CDC) description of the antimicrobial-resistant pathogens, Carbapenem Resistant Enterobacteriaceae such as *Klebsiella* species, *Escherichia coli* (*E. coli*) and *Enterobacter* species pose a substantial threat at the global level.[11].With this in mind, our study aims for a thorough review of resistance profiles of *Enterobacteriaceae* isolates from Blood stream infections in a tertiary healthcare center of western Uttar Pradesh.

Materials and Methods: The study was conducted at Jawaharlal Nehru Medical College and Hospital, Aligarh, a tertiary care institute in western Uttar Pradesh. Analysis of Blood culture

isolates was done for their antimicrobial susceptibility, over a period of one year that is January 2022-December 2022.

Sample Grouping: Blood culture was performed by BacT/ALERT automated system and positive isolates were first grouped into Gram positive, Gram negative and Fungal. Among the gram negative, members of the Enterobacteriaceae were reviewed for their resistance profile. **Antimicrobial Susceptibility Testing:** AST was done Kirby Bauer Disc Diffusion method as well as VITEK automated system wherein the isolates were exposed to several antibiotics as per the CLSI guidelines [12]

Results

Out of the 3441 blood culture samples, 505 (14.67%) were positive. There were 155/505 (30.69%) cases of Gram Positive,114/505 (22.57%) cases of Candida species and 236/505(46.73%) species of Gram-Negative Bacteria.

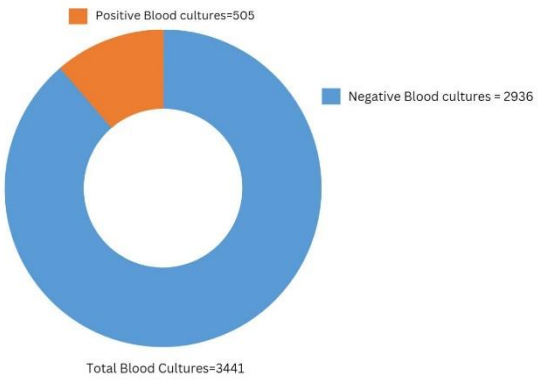

Fig 1. Positive blood cultures

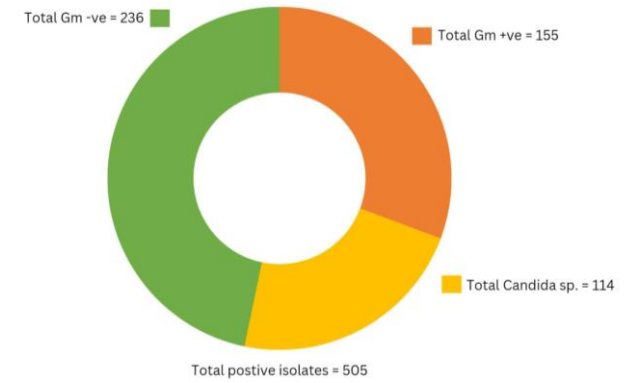

Fig 2. Distribution of isolates

Out of the 236 Gram Negative isolates,151(63.98%) were *Enterobacteriaceae* and the rest were non-fermenters like *Pseudomonas, Acinetobacter* and *Burkholderia.*

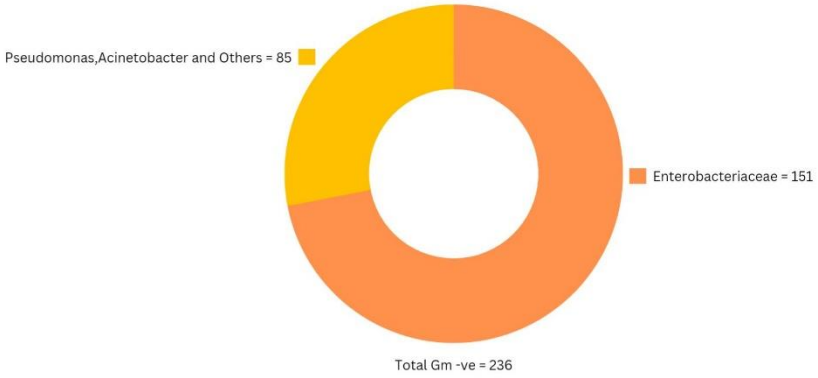

Fig 3. Gram Negative isolates overall

Among the *Enterobacteriaceae*, 99/151(65.56%) were *Klebsiella* isolates, 33/151 (21.85%) were *E. coli* isolates, 15/151(9.93%) were *Salmonella* isolates and 4/151(2.65%) were *Enterobacter cloacae* isolates

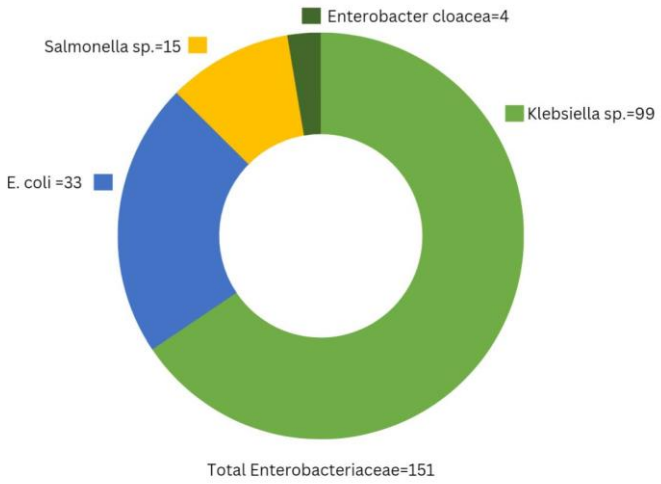

Fig 4. *Enterobacteriaceae* isolates overall

Among 99 *Klebsiella* isolates, 91/99 (90.09%) were resistant to Aminoglycosides like Amikacin or Gentamicin; 85/99(84.15%) were resistant to one or several 2nd and 3rd generation Cephalosporins; 84/99(83.16%) were resistant to the combination of Amoxicillin and Clavulanic acid;81/99(80.19%) were resistant to Tetracyclines; 81/99(80.19%) were resistant to Carbapenems;79/99(78.21%)were resistant to Cotrimoxazole, 41/99(40.59%) were resistant

Colistin and a whopping 24/99(23.76%)were Pan-drug resistant.

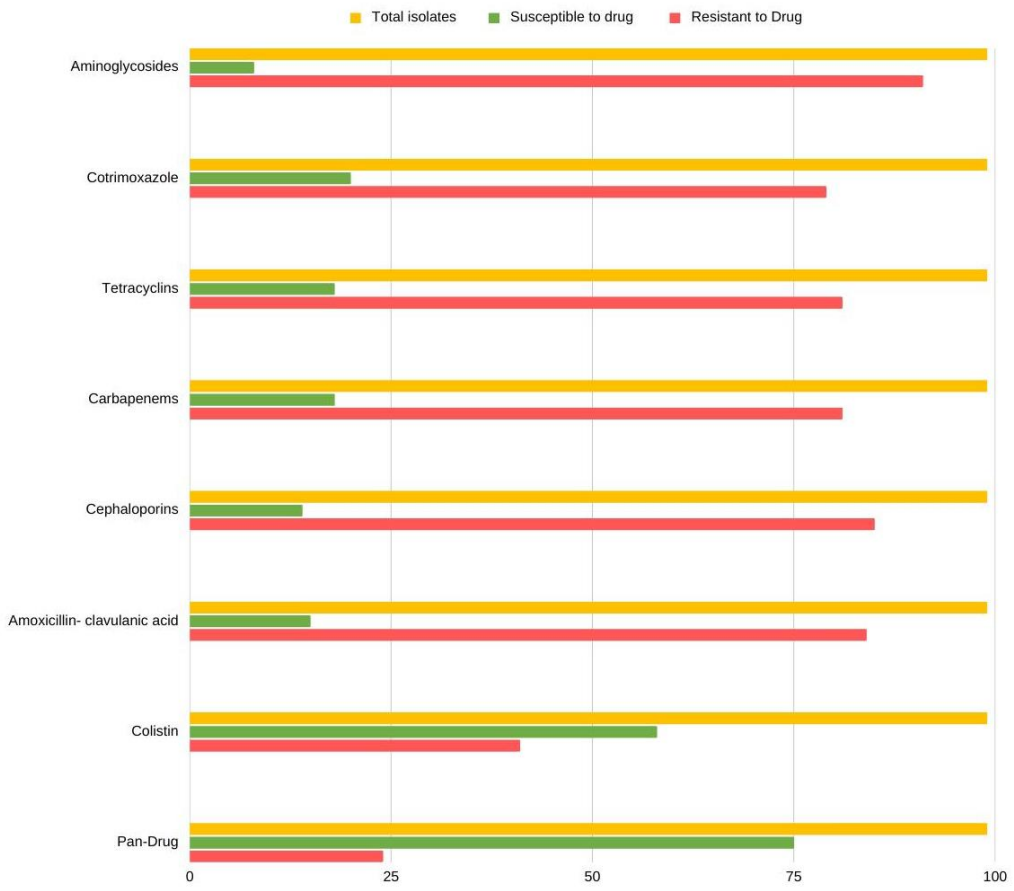

Fig 5. Resistance profile in *Klebsiella*

Among the 33 *E. coli* isolates, 27/33 (81.81%) were resistant to Aminoglycosides, 25/33(75.75%) are resistant to Carbapenems, 24/33(72.72%) were resistant to Cephalosporins, 17/33(51.51%) were resistant to Amoxicillin Clavulanic acid combinations,15/33(45.45%) were resistant to Tetracyclines, 12/33(36.36%) were resistant to Cotrimoxazole and 6/33(18.18%) were resistant to Colistin.

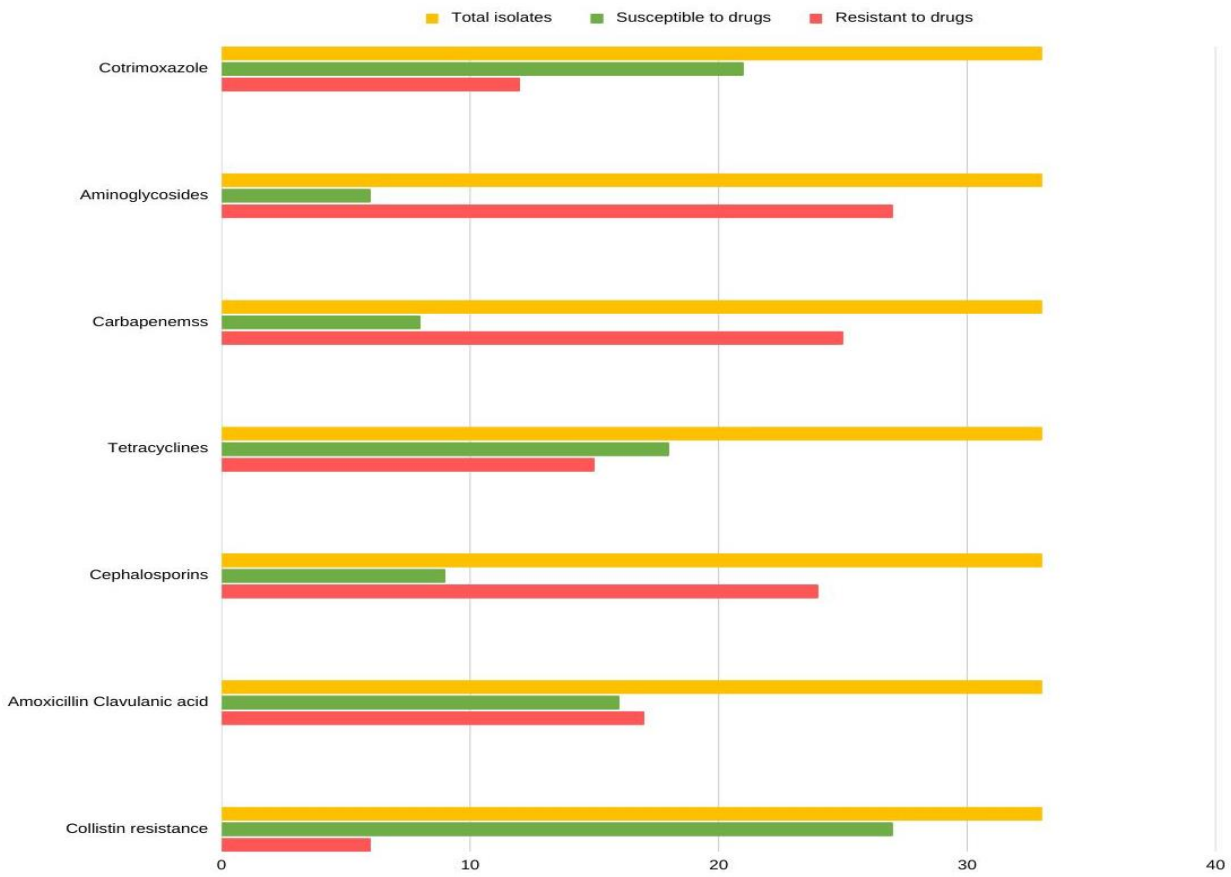

Fig 6. Resistance profile of *E. coli*

Among the 15 *Salmonella* isolates, 11/15(73.33%) were resistant to combinations of Piperacillin and Tazobactam,10/15(66.67%) were resistant to 3rd generation Cephalosporins, 10/15(66.67%) were resistant to Carbapenems, 9/15(60%) were resistant to Tetracyclines, 7/15(46.67%) were resistant to Cotrimoxazole,6/15(40%) were resistant to Aminoglycosides mostly Amikacin and 3/15 (20%) were Colistin resistant.

Fig. 7 Resistance profile of *Salmonella*

Carbapenem Resistant Enterobacteriaceae (CRE) has been prevalent worldwide and our data happens to reflect the same, where in 25/33(67%) of *Salmonella* isolates,25/33 (76%) of *E. coli* isolates and 81/99 (82%) of *Klebsiella pneumoniae* isolates were found to be resistant to Carbapenems.

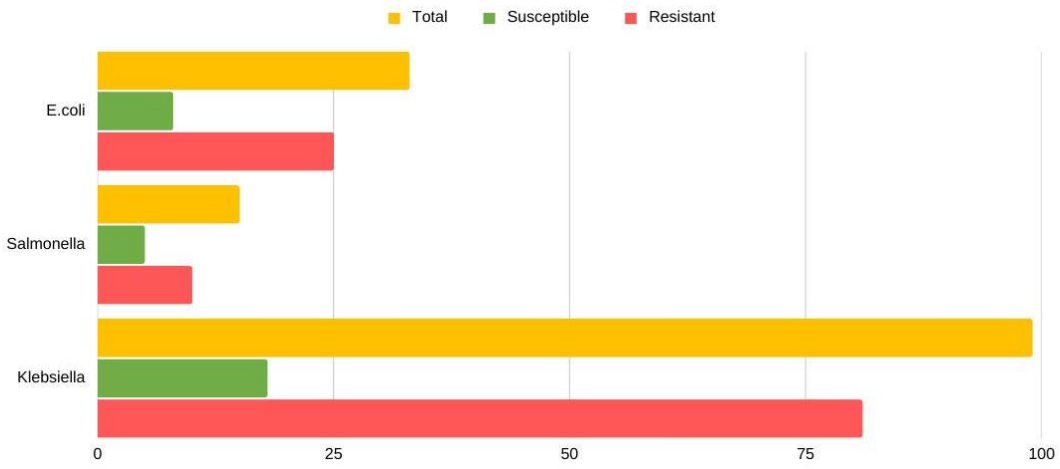

Fig. 8. Resistance to Carbapenems

Discussion: There is a high propensity of Blood stream Infections progressing to septic shock and multi-organ failure, increasing the risk of mortality by 40%, especially when gram negative organisms are implicated.[13] Therefore the need of a prompt and aggressive therapy regimen is emphasized by microbiologists' time and again. The appropriate “time window” for administration of medication is <6hrs, some even arguing that the first hour is most critical.[14]

The management of BSIs associated with Enterobacteriaceae family emerges as a challenge as this group is known for producing ESBLs. Extended Spectrum Beta Lactamases are enzymes that hydrolyze most beta lactams rendering Penicillins, most Cephalosporins and monobactams ineffective. Since the plasmid that encodes ESBL’s is frequently known to carry genes conveying resistances towards other antibiotic groups, these *Enterobacteriaceae* are often found to be resistant towards Aminoglycosides and Tetracyclines as well.[15]. Carbapenems are therefore considered the centerpiece in case of BSI’s caused by ESBL producing Enterobacteriaceae.[16] However studies have pointed out that increased production of AmpC-mediated β-lactamases or extended-spectrum β-lactamases (ESBLs) in organisms, porin mutations [17,18]as well as synthesis of carbapenemases itself has conferred resistance against Carbapenems as well. Resistance among Enterobacteriaceae is an issue demanding great concern considering the frequency by which they cause infections.[19] These organisms, especially Carbapenem Resistant Enterobacteriaceae result in prolonged hospitalization, higher costs incurred, and also higher mortality as compared to their susceptible counterparts.[20]Presence of these microbes possess a threat of emergence of other resistant organisms via mobile genetic elements like plasmids being shared.[21] The resistance profiles of our sample isolates aptly reflect the fact there are virtually no drugs left. Therefore, the development of new drugs is a global need.

Conclusion*:* Given the therapeutic complications of Blood stream infections, it is implied that better health strategies be developed to prevent them in the first place. Use of sterile barrier precautions for all patients, appropriate skin antiseptics, especially while inserting central line catheters and frequent handwashing are to name a few. Antimicrobial Stewardship Programmes too, are imperative.

References:

1. Garner, J. S., Jarvis, W. R., Emori, T. G., Horan, T. C., & Hughes, J. M. (1991). CDC definitions for nosocomial infections 1988. *Zeitschrift fur arztliche Fortbildung*, *85*(17), 818-827.
2. Lenz R, Leal JR, Church DL, Gregson DB, Ross T, Laupland KB. The distinct category of healthcare associated bloodstream infections. BMC infectious diseases. 2012 Dec;12(1):1-6.
3. Exline, M. C., Ali, N. A., Zikri, N., Mangino, J. E., Torrence, K., Vermillion, B., ... & Sopirala, M. M. (2013). Beyond the bundle-journey of a tertiary care medical intensive care unit to zerocentral line-associated bloodstream infections. *Critical care*, *17*, 1-13.
4. Parameswaran, R., Sherchan, J. B., Mukhopadhyay, C., & Vidyasagar, S. (2011). Intravascular catheter-related infections in an Indian tertiary care hospital. *The Journal of Infection in Developing Countries*, *5*(06), 452-458.
5. Bharadwaj, R., Bal, A., Kapila, K., Mave, V., & Gupta, A. (2014). Blood stream infections. *BioMed research international*, *2014*.
6. Datta, S., Wattal, C., Goel, N., Oberoi, J. K., Raveendran, R., & Prasad, K. (2012). A ten year analysis of multi-drug resistant blood stream infections caused by Escherichia coli & Klebsiella pneumoniae in a tertiary care hospital. *The Indian journal of medical research*, *135*(6), 907.
7. Kaur, R., Goyal, R., Dhakad, M. S., Bhalla, P., & Kumar, R. (2014). Epidemiology and virulence determinants including biofilm profile of Candida infections in an ICU in a tertiary hospital in India. *Journal of Mycology*, *2014*.
8. Centers for Disease Control and Prevention. (2019). Antibiotic resistance threats in the United States, 2019. Atlanta, GA: US Department of Health and Human Services, CDC; 2019.
9. De Angelis, G., Del Giacomo, P., Posteraro, B., Sanguinetti, M., & Tumbarello, M. (2020). Molecular mechanisms, epidemiology, and clinical importance of β-lactam resistance in Enterobacteriaceae. *International journal of molecular sciences*, *21*(14), 5090.
10. Van Duin, D., & Paterson, D. L. (2016). Multidrug-resistant bacteria in the community: trends and lessons learned. *Infectious disease clinics*, *30*(2), 377-390.
11. Tilahun, M., Kassa, Y., Gedefie, A., & Ashagire, M. (2021). Emerging carbapenem-resistant Enterobacteriaceae infection, its epidemiology and novel treatment options: a review. *Infection and drug resistance*, 4363-4374.
12. Hsueh, P. R., Ko, W. C., Wu, J. J., Lu, J. J., Wang, F. D., Wu, H. Y., ... & Teng, L. J. (2010). Consensus statement on the adherence to Clinical and Laboratory Standards Institute (CLSI) Antimicrobial Susceptibility Testing Guidelines (CLSI-2010 and CLSI-2010-update) for Enterobacteriaceae in clinical microbiology laboratories in Taiwan. *Journal of Microbiology, Immunology and Infection*, *43*(5), 452-455.
13. Conn, J. R., Catchpoole, E. M., Runnegar, N., Mapp, S. J., & Markey, K. A. (2017). Low rates of antibiotic resistance and infectious mortality in a cohort of high-risk hematology

patients: A single center, retrospective analysis of blood stream infection. *PLoS One*, *12*(5), e0178059.

14. Kang, C. I., Kim, S. H., Park, W. B., Lee, K. D., Kim, H. B., Kim, E. C., ... & Choe, K. W. (2005). Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrobial agents and chemotherapy*, *49*(2), 760-766.
15. Conn, J. R., Catchpoole, E. M., Runnegar, N., Mapp, S. J., & Markey, K. A. (2017). Low rates of antibiotic resistance and infectious mortality in a cohort of high-risk hematology patients: A single center, retrospective analysis of blood stream infection. *PLoS One*, *12*(5), e0178059.
16. Paterson, D. L. (2000). Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs). *Clinical Microbiology and Infection*, *6*(9), 460-463.
17. Bradford, P. A., Urban, C., Mariano, N., Projan, S. J., Rahal, J. J., & Bush, K. (1997). Imipenem resistance in Klebsiella pneumoniae is associated with the combination of ACT-1, a plasmid-mediated AmpC beta-lactamase, and the foss of an outer membrane protein. *Antimicrobial agents and chemotherapy*, *41*(3), 563-569.
18. Chow, J. W., & Shlaes, D. M. (1991). Imipenem resistance associated with the loss of a 40 kDa outer membrane protein in Enterobacter aerogenes. *Journal of Antimicrobial Chemotherapy*, *28*(4), 499-504.
19. Gupta, N., Limbago, B. M., Patel, J. B., & Kallen, A. J. (2011). Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. *Clinical infectious diseases*, *53*(1), 60-67.
20. Patel, G., Huprikar, S., Factor, S. H., Jenkins, S. G., & Calfee, D. P. (2008). Outcomes of carbapenem-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. *Infection Control & Hospital Epidemiology*, *29*(12), 1099-1106.
21. Watanabe, M., Iyobe, S., Inoue, M., & Mitsuhashi, S. (1991). Transferable imipenem resistance in Pseudomonas aeruginosa. *Antimicrobial agents and chemotherapy*, *35*(1), 147-151.