International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 19s, 2025
https://www.theaspd.com/ijes.php

Antimicrobial Resistance Patterns Of Enterobacter Cloacae Complex And Enterobacter Aerogenes Strains Isolated From Clinical Specimens: A Five-Year Surveillance Study

Balungile Shezi[1*,2], **Pakiso Makhoahle**[2]

[1*]Clinical Pathology, Pathcare laboratories, Hermanus 7200, Western Cape, South Africa
[2]Department of Health Science, Center for Quality of Health and Living, Faculty of Health and Environmental Sciences, Central University of Technology, Bloemfontein 9301, Free State, South Africa
*Corresponding author: Balungile Shezi
*E-mail: pmakhoahle@cut.ac.za

ABSTRACT

Introduction: *Antimicrobial resistance has become a worldwide problem due to the escalating evolution of resistance combined with a reduced antimicrobial pipeline. The genus Enterobacter is one of the primary pathogens that cause nosocomial infections because of its numerous resistance mechanisms and capacity to "evade" antimicrobial therapy.*
Aim: *The study assessed the antimicrobial profile of the two mostly isolated Enterobacter spp., Enterobacter aerogenes and Enterobacter cloacae complex.*
Methodology: *A retrospective data analysis of patients reported at Grey's; Harry Gwala and Northdale hospitals from 2018-2021 was performed. Target sample was specifically for sensitivity profile of Enterobacter aerogenes and Enterobacter cloacae complex from both inpatients and outpatients infected by the gram-negative ESKAPE reported at those 3 hospitals. Following health sciences ethics committee (HSREC) and National Health Laboratory Service (NHLS) approvals, data were retrieved from the NHLS Central Data Warehouse through the Academic Affairs and Research Management Systems (AARMS).*
Results: *A total of 1746 non-duplicate Enterobacter spp. strains isolated from inpatients and outpatients were retrieved, 86% were Enterobacter cloacae complex and the remaining 13.7% were Enterobacter aerogenes.*
Discussion: *Enterobacter cloacae complex showed minimal resistance to all tested carbapenems with meropenem being the highest of the three at 5, 4%. Enterobacter aerogenes showed a similar pattern as far as carbapenems resistance are concerned. Although the resistance to carbapenems such as imipenem and meropenem were found to be relatively low in the Enterobacter species, analysis also showed an increasing trend post-COVID-19 era.*
Conclusion and recommendations: *This analysis reveals not so alarming but significant changes in resistance rates for several antibiotics, particularly in the A. cloacae complex. Providing ongoing education and training for healthcare workers on the importance of antimicrobial agent stewardship and infection control practices is paramount to prevent further increase in resistance. Future research should aim to expand surveillance networks to include more hospitals and regions within South Africa. This would provide a more comprehensive understanding of antimicrobial resistance patterns and facilitate timely interventions.*

Keywords: PMB; antimicrobial agents; resistance trends; Enterobacter cloacae complex; Enterobacter aerogenes.

INTRODUCTION

Antimicrobial resistance (AMR) is a major health and financial concern, especially the Enterobacteriaceae, which are third-generation bacteria that are resistant to cephalosporins, carbapenem, and other drugs (WHO, 2023). The misuse of antibiotics, as well as the restricted availability of novel antimicrobial agents, have contributed to the rise in antimicrobial resistance (Hou et al., 2023). Global estimates show that the number of fatalities directly linked to AMR increased to over 1,2 million in 2019, and if no action is taken to manage AMR, this number is expected to rise to almost 10 million deaths annually by 2050 (Tang et al., 2023). Surveillance studies enable the monitoring of the establishment of antibiotic resistance, the implementation of control measures, and the formulation of the antimicrobial usage guidelines for patients (Intra et al., 2023).

Enterobacter species are Gram-negative opportunistic bacilli belonging to the Enterobacteriaceae family. They cause septicemia, severe urinary tract infections (UTIS), and pneumoniae in intensive care unit (ICU) patients that are on mechanical ventilation, leukemic patients, diabetic patients, premature infants, and traumatized patients (Annavajhala et al., 2019). Enterobacter species belong to the ESKAPE group, which also includes Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species (Yan et al., 2024), which is known to be the most common cause of nosocomial infections. As a result, the World Health Organization (WHO) added Enterobacter spp. to the priority list of pathogens that require research and development of new antibiotics (Davin-Regli et al., 2019). Enterobacter spp. has an intrinsic resistance to broad-spectrum cephalosporins and ampicillin and have become resistant to numerous antimicrobials such as carbapenems and third generation cephalosporins, making the selection of appropriate therapy difficult. This resistance is caused by the acquisition of genetic mobile elements (Quraishi et al., 2019). A few studies on antimicrobial resistance in Enterobacter spp. have been reported, particularly over a lengthy period (Jiménez-Guerra et al., 2020; Liu et al., 2021).

A retrospective microbiological data obtained from the National Health Laboratory Service Central Data Warehouse via the Academic Affairs and Research Management Systems over a 5-year period (2017–2021) were examined to determine sensitivity patterns of Enterobacter aerogenes and Enterobacter cloacae strains. Understanding the best diagnosis is important to evaluate resistance trends for the best patient treatment failure.

ENTEROBACTER CLOACAE COMPLEX

Enterobacter cloacae, the third-ranked Enterobacteriaceae, produces low amounts of inducible AmpC β-lactamase, which makes it naturally resistant to ampicillin, amoxicillin-clavulanate, first-generation cephalosporins, and cefoxitin (Yan et al., 2024). Certain β-lactam antibiotics, such as aztreonam and third generation cephalosporins, have the ability to strongly induce this cephalosporinase. Except for cefepime, resistance to broad-spectrum cephalosporins can result from overexpression of these enzymes. Therefore, serious thought should be given to the clinical use of third generation cephalosporins in treating severe infections caused by Enterobacter cloacae, even when they exhibit sensitivity (Guerin et al., 2015). Additionally, the number of carbapenem-resistant E. cloacae (CR-ECL) is growing (Cassini et al., 2019).

ENTEROBACTER AEROGENES

Although Enterobacter aerogenes has long been thought of as an opportunistic pathogen, there has been a recent surge of interest in this organism, mostly because of the appearance of strains that are carbapenem-resistant as well as multi-drug resistant (Merhi et al., 2023). This could be because E. aerogenes has already been found to have acquired antibiotic resistance genes through mobile elements like plasmids and conjugative integrative elements. However, changes affecting membrane permeability and chromosomal overexpression of AmpC β-lactamase (blaCMY-2 and blaDHA-1) are thought to be the primary causes of carbapenem resistance in this species (Malek et al., 2019; Meini et al., 2019). The high frequency of outbreaks of this emergent pathogen is continuously reported, and some of these outbreaks have been linked to significant fatality rates (Hao et al., 2019) in various clinical settings worldwide, including intensive care (Meini et al., 2019), geriatric, and neonatal units (Baier-Grabner et al., 2022; Hallbäck et al., 2023).

RESULTS

A total of 1746 non-duplicate Enterobacter spp. strains isolated from inpatients and outpatients' data were retrieved, 1506 were Enterobacter cloacae complex (86%) and 240 were Enterobacter aerogenes isolates (13.7%). Enterobacter species had the highest resistance to amoxicillin clavulanic acid and cefotaxime with over 98% but were still highly susceptible to the currently preferred antimicrobials such as tobramycin (0, 6%), colistin (0,3%) and ertapenem (3,3%) on average.

Enterobacter cloacae complex, as shown in (Figure 1A) had a very high antimicrobial susceptibility rate (52, 1%), which qualifies it as the least problematic/ worrisome group of sub-species in the Enterobacter family. However, this pathogen's extremely low susceptibility rate against amoxicillin clavulanic acid (0, 01%) cannot be ignored. Similar to the E. cloacae complex, E. aerogenes showed very little overall resistance to most antimicrobial agents tested for, with amikacin and tobramycin showing the least resistance (both at 0,8%), as shown in Figure 7d. This makes these two antimicrobial agents the most effective after colistin (0%) against Enterobacter species.

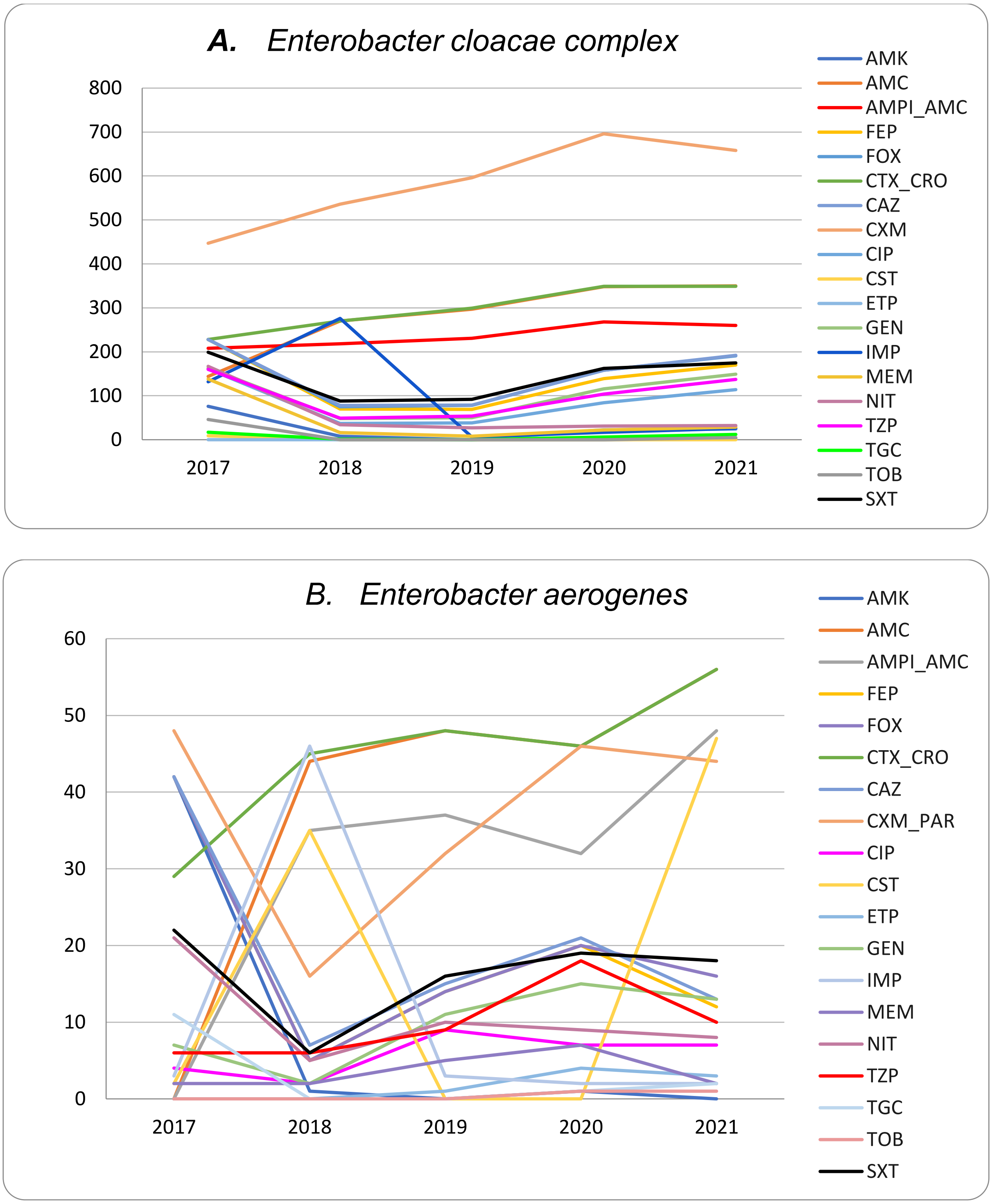

Figure 1A-B: Annual resistance trends of 19 antimicrobial agents in PMB during the study period. A- Enterobacter cloacae complex and B- Enterobacter aerogenes.

Antimicrobial agents' abbreviations: AMK = amikacin. TGC = tigecycline. AMC = Amoxicillin clavulanic acid. AMPI_AMC = Ampicillin amoxicillin. FEP = cefepime. CTX_CRO = cefotaxime ceftriaxone. FOX = cefotaxime. CAZ = ceftazidime. CXM = cefuroxime (oral and parenteral). CIP = ciprofloxacin. CST = colistin. ETP =

ertapenem. GEN = gentamicin. IMP = imipenem. MEM = meropenem. NIT = nitrofurantoin. TZP = piperacillin/tazobactam; TOB = tobramycin. SXT - trimethoprim/sulfamethoxazole.

DISCUSSION

Enterobacter cloacae complex showed minimal resistance to all tested carbapenems (ertapenem, imipenem, and meropenem) with a resistance of 3, 2%, 4, 8% and 5, 4%, respectively. This low resistance picture towards carbapenems is like E. aerogenes. These results are consistent with a similar study done in KZN between 2011 and 2015, which states that Enterobacter spp. was shown to have an average accumulative resistance rate of 5% to available carbapenems (Ramsamy et al., 2018). In this study, E. cloacae showed a higher resistance of 16% to ciprofloxacin than E. aerogenes, with only 8%.

Although ciprofloxacin resistance varied, it generally showed an upward trend. This trend may be because carbapenems were not really affected by ESBL previously, even though there has been a slight increase in resistance lately, which results from the fact that Enterobacter spp. has now developed beta-lactamases which hydrolyze the beta-lactam ring seen in cephalosporins and penicillin's (Ramirez and Giron, 2023). This increased resistance may also be a result of multiple plasmid-mediated enzymes, leading to the development and accessible horizontal transfer of widespread resistance.

Even though the rate of antimicrobial resistance between the Enterobacter species isn't alarming, statistical analysis indicated significant changes in antimicrobial resistance trends for certain antimicrobials pre- and post-COVID-19, particularly for the E. cloacae Complex (figure 1B). These trends suggest increased resistance rates, highlighting the need for continued surveillance and intervention.

CONCLUSION AND RECOMMENDATIONS

This study provides a comprehensive analysis of the resistance trends of Enterobacter aerogenes and Enterobacter cloacae complex pathogens in PMB state hospitals over five years. This analysis reveals some significant changes in resistance rates for several antibiotics, particularly in the A. cloacae complex.

Building on the current study, enhancing Antimicrobial Stewardship Programs across healthcare facilities is essential for optimizing antibiotic use and minimizing the development of resistance. Future efforts should focus on training healthcare professionals, implementing antibiotic prescribing guidelines, and monitoring antibiotic use. Future studies should incorporate Whole Genome sequencing to identify specific resistance genes and mutations responsible for AMR in the ESKAPE pathogens. Conducting longitudinal studies to assess the long-term impact of the COVID-19 pandemic on AMR trends will be important.

REFERENCES

1. Annavajhala, M.K, Gomez-Simmonds, A, & Uhlemann, A.C., 2019. Multidrug-Resistant Enterobacter cloacae Complex Emerging as a Global, Diversifying Threat. Frontiers in microbiology, 10(44), pp.3389.
2. Baier-Grabner, S, Equiluz-Bruck, S, Endress, D, Blaschitz, M, Schubert, S, Indra, A, Fudel, M, Frischer, T, and Götzinger, F., 2022. A yersiniabactin-producing Klebsiella aerogenes strain causing an outbreak in an Austrian neonatal intensive care unit. The pediatric infectious disease journal, 41(7), pp.593–599.
3. Cassini, A, Högberg, L.D, Plachouras, D, Quattrocchi, A, Hoxha, A, Simonsen, G.S, Colomb-Cotinat, M, Kretzschmar, M.E, Devleesschauwer, B, Cecchini, M, Ouakrim, D.A, Oliveira, T.C, Struelens, M.J, Suetens, C, Monnet, D.L, and Burden of AMR Collaborative Group., 2019. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. The Lancet. Infectious diseases, 19(1), pp56–66.
4. Davin-Regli, A., Lavigne, J.P., and Pagès, J.M., 2019. Enterobacter spp.: Update on taxonomy, clinical aspects, and emerging antimicrobial resistance. Clinical Microbiology Reviews, 32(4), e00002-19.
5. Guérin, F, Isnard, C, Cattoir, V, Giard JC., 2015. Complex Regulation Pathways of AmpC-Mediated β-Lactam Resistance in Enterobacter cloacae Complex. ASM Journals Antimicrobial Agents and Chemotherapy 59(12).
6. Hallbäck, E.T, Johnning, A, Myhrman, S, Studahl, M, Hentz, E, Elfvin, A, and Adlerberth, I., 2023. Outbreak of OXA-48-producing Enterobacteriaceae in a neonatal intensive care unit in Western Sweden. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology, 42(5), pp.597–605.

7. Hao, M, Shen, Z, Ye, M, Hu, F, Xu, X, Yang, Y, Wu, S, Lin, D, Qin, X, and Wang, M., 2019. Outbreak of Klebsiella pneumoniae carbapenemase-producing Klebsiella aerogenes strains in a tertiary hospital in China. Infection and drug resistance, 12, pp.3283–3290.
8. Hou, J., Long, X., Wang, X., Li, L., Mao, D., Luo, Y., & Ren, H., 2023. Global trend of antimicrobial resistance in common bacterial pathogens in response to antibiotic consumption. Journal of hazardous materials, 442, pp.130042.
9. Intra, J, Carcione, D, Sala, R.M, Siracusa, C, Brambilla, P, and Leoni, V., 2023. Antimicrobial Resistance Patterns of Enterobacter cloacae and Klebsiella aerogenes Strains Isolated from Clinical Specimens: A Twenty-Year Surveillance Study. Antibiotics, 12(4), pp.775.
10. Jiménez-Guerra, G, Borrego-Jiménez, J, Gutiérrez-Soto, B, Expósito-Ruiz, M, Navarro-Marí, J. M, and Gutiérrez-Fernández, J., 2020. Susceptibility evolution to antibiotics of Enterobacter cloacae, Morganella morganii, Klebsiella aerogenes and Citrobacter freundii involved in urinary tract infections: an 11-year epidemiological surveillance study. Evolución de la sensibilidad a los antibióticos de Enterobacter cloacae, Morganella morganii, Klebsiella aerogenes y Citrobacter freundii causantes de infecciones del tracto urinario: un estudio de vigilancia epidemiológica de 11 años. Enfermedades infecciosas y microbiologia clinica (English ed.), 38(4), pp.166–169.
11. Liu, S, Fang, R, Zhang, Y, Chen, L, Huang, N, Yu, K, Zhou, C, Cao, J, and Zhou, T., 2021. Characterization of resistance mechanisms of Enterobacter cloacae Complex co-resistant to carbapenem and colistin. BMC microbiology, 21(1), pp.208.
12. Malek, A, McGlynn, K, Taffner, S, Fine, L, Tesini, B, Wang, J, Mostafa, H, Petry, S, Perkins, A, Graman, P, Hardy, D, and Pecora, N., 2019. Next-generation-sequencing-based hospital outbreak investigation yields insight into Klebsiella aerogenes population structure and determinants of carbapenem resistance and pathogenicity. Antimicrobial agents and chemotherapy, 63(6), e02577-18.
13. Meini, S, Tascini, C, Cei, M, Sozio, E, and Rossolini, G.M., 2019. AmpC β-lactamase-producing Enterobacterales: what a clinician should know. Infection, 47(3), pp.363–375.
14. Merhi, G, Amayri, S, Bitar, I, Araj, G.F, and Tokajian, S., 2023. Whole genome-based characterization of multidrug resistant Enterobacter and Klebsiella aerogenes Isolates from Lebanon. Microbiology spectrum, 11(1), e0291722.
15. Quraishi, M, Saleh, A.A, Roy, C.K, Afroz, F, and Mohiuddin, G.M., 2019. Antimicrobial resistance pattern of Enterobacter species isolated from different clinical specimens in a tertiary care hospital of Bangladesh. Bangladesh Journal of Medical Microbiology, 13(2), pp.3-6.
16. Tang, K.W.K., Millar, B.C., and Moore, J.E., 2023. Antimicrobial Resistance (AMR). Br J Biomed Sci, 80, pp.11387.
17. World Health Organisation, 2023. Antimicrobial resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. [Accessed:27 October 2024].
18. Yan, S, Sun, Z, Yang, Y, Zhu, D, and Chen, Z., 2024. Changing antimicrobial resistance profile of Enterobacter spp. isolates in hospitals across China: a seven-year analysis from the CHINET antimicrobial resistance surveillance program (2015–2021). One Health Adv. 2, (11).