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ORIGINAL RESEARCH

Laboratory-based surveillance of the susceptibility of carbapenemase-producing *Enterobacterales* to ceftazidime-avibactam: a preliminary antimicrobial stewardship initiative

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Background: In vitro susceptibility testing for the antibiotic ceftazidime-avibactam (CZA) commenced at one of the private diagnostic laboratories in South Africa (SA) in 2020. The drug was registered in SA in September 2021. While there is a paucity of quantitative data on CZA susceptibility in SA, Brink et al.[11] noted increasing resistance to the drug in the country in 2022. This study provided surveillance of carbapenemase-producing *Enterobacterales* (CPE) susceptibility to CZA using data observed over two years.

Objective: This study aimed to determine if there is a developing trend of CPE resistance to CZA so that better stewardship and infection control measures can be implemented to safeguard the effective use of the drug.

Study design and methods: This was a longitudinal quantitative study. CZA susceptibility patterns of the OXA-48 subtype of CPE were observed and compared over two years to detect any resistance. Mass spectrometry was used to identify the isolates, and the polymerase chain reaction (PCR) assay and Kirby-Bauer (KB) methods were used to determine the carbapenemase type and CZA susceptibility, respectively.

Results: A total of 495 OXA-48 isolates were selected from 2020 and a total of 439 from 2021. Of the isolates, 6% from 2020 were resistant, while 9% from 2021 were resistant.

Conclusion: This preliminary observational study observed the beginning of a resistance trend between the years of 2020 and 2021.

Keywords: Avycaz, Zavicefta, South Africa, antimicrobial resistance, OXA-48

Introduction

The emergence of multidrug-resistant (MDR) pathogens is one of the greatest health crises that our society is facing.[1] Among MDR pathogens are carbapenem-resistant *Enterobacterales* (CRE) and carbapenemase-producing *Enterobacterales* (CPE (CPE). CRE are *Enterobacterales* resistant to some or all carbapenem antibiotics (i.e. imipenem, meropenem, doripenem, and ertapenem).[2] CPE, on the other hand, are CRE that achieve carbapenem resistance by producing one or more carbapenemase enzymes. These enzymes hydrolyse and inactivate antimicrobials such as penicillins, cephalosporins, monobactams, and carbapenems, making them ineffective against the respective pathogens.[2] Among the different classes of carbapenemases is the class D oxacillinase (OXA) enzymes – most commonly OXA-48.[2] A study conducted on bacteraemia-causing CPE isolates from academic hospitals in South Africa (SA) between 2019 and 2020 revealed OXA-48 to be the most common carbapenemase, with *Klebsiella pneumoniae* being the predominant species.[3]

Infections caused by CPE have been highlighted as a global threat, and CPE have been categorised by the World Health Organization (WHO) as critical pathogens.[4] As one of the measures to treat these super-bugs, the ceftazidime-avibactam (CZA) drug was approved by the Food and Drug Administration (FDA) in 2015.[5] This drug is a combination of ceftazidime (a third-generation cephalosporin) and avibactam (a novel non-β-lactam β-lactamase inhibitor).[6] The Infectious Diseases Society of America (IDSA) has recommended CZA as a first-line treatment against infections caused by OXA-48-producing CPE.[7] In a clinical trial conducted in the USA, patients infected with OXA-48-producing pathogens demonstrated successful clinical outcomes when treated with CZA.[8] However, susceptibility to CZA is low in the presence of metallo-β-lactamase (MBL) carbapenemases.[9] Hence, isolates harbouring only the OXA-48 enzyme were included in this study.

In 2020, a private diagnostic laboratory in Durban, SA, commenced in vitro susceptibility testing of the CZA drug against CPE. In this study, susceptibility results of OXA-48 CPE were compiled over two years and then observed for any resistance trend. The aim was to determine if there is a developing trend of OXA-48 CPE resistance to CZA.

Methods

Study design and setting

In this longitudinal quantitative study, laboratory-based surveillance was employed to determine the pattern of OXA-48 susceptibility to CZA over two years. The study was carried out in Durban, KwaZulu-Natal (KZN), on isolates and data collected from different areas around the KZN province and analysed at a private laboratory in Durban.

Ethical considerations

Ethical approval was granted by the Durban University of Technology Institutional Research Ethics Committee (IREC number 098/22). Gatekeeper permission was granted by the Lancet Laboratories Publications Board on 20 July 2022. All data was anonymised before analysis, thus maintaining patient confidentiality.

Inclusion and exclusion criteria

Only OXA-48 isolates were selected for this study: 495 isolates from 2020 and 439 from 2021.

Laboratory analysis

The Kirby-Bauer (KB) disc diffusion method was used to test for CZA susceptibility. This method involved culture of the isolates on agar plates with antibiotic-impregnated discs placed in the centre. The plates were then incubated at 37 °C in an aerobic incubator. After 24 hours, the plates were examined for a zone of growth inhibition around the antibiotic disc (Figure 1). Susceptibility testing was interpreted using the 2020 Clinical and Laboratory Standards Institute (CLSI) guidelines for the 2020 population and the 2021 CLSI guidelines for the 2021 population.[10,20] According to both standards, resistant/non-susceptible refers to a zone size diameter of less than or equal to 20 mm, and susceptible refers to a zone size diameter of greater than or equal to 21 mm.[10]

The type of carbapenemase produced by each isolate was determined using the Cepheid® GeneXpert® polymerase chain reaction (PCR) assay. The phenotypic identification of each isolate was determined using either matrix-assisted laser desorption/ionisation mass spectrometry (MALDI-MS) or the VITEK® 2 system. Of the total 934 isolates used in this study, there were five *Citrobacter freundii*, 18 *E. coli,* 10 *Enterobacter* species, 752 *Klebsiella pneumoniae,* one *Klebsiella oxytoca,* 47 *Serratia marcescens,* and one *Morganella morganii* isolate.

Statistical analysis

Percentage resistance was calculated as follows:

The number of resistant OXA-48 isolates ÷ total number of OXA-48 isolates × 100.

Results

Of the 495 isolates tested in 2020, 30 were resistant. Of the 439 tested in 2021, 40 were resistant. This is a percentage resistance of 6% and 9%, respectively. The graph in Figure 2 displays the decrease in CZA susceptibility between 2020 and 2021.

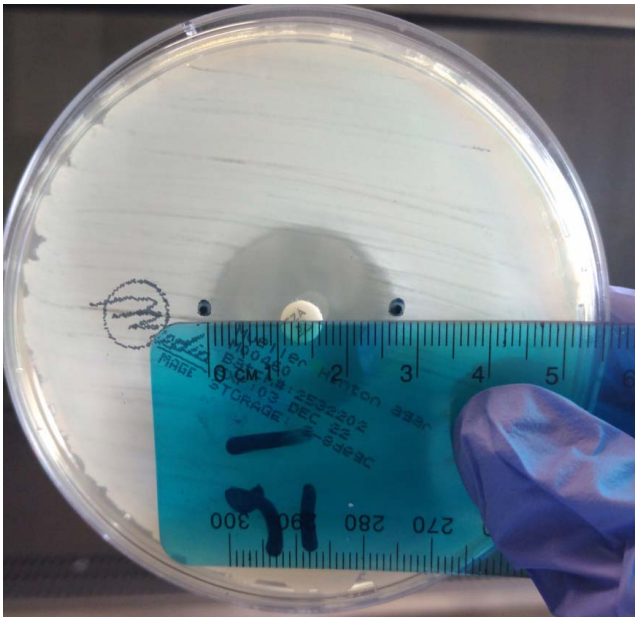

Figure 1: Measurement of inhibition zone around antibiotic disc

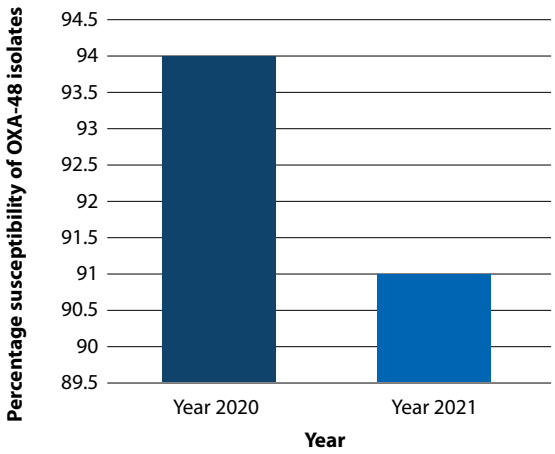

Figure 2: Percentage susceptibility of OXA-48 to CZA between 2020 and 2021

Discussion

Carbapenems are antibiotics initially approved in 1985.[4] However, their overuse has led to the development of CPE.[4] Among the CPE types, OXA-48 is the most commonly reported globally.[4] As the global health system wages war to curb the rise of antimicrobial resistance (AMR), there is a simultaneous ongoing battle to develop new drugs to fight these MDR organisms.[1]

CZA is one of the first second-generation β-lactam inhibitor combination (BLIC) drugs to be registered in SA.[11] In a multicentre cohort study conducted in Saudi Arabia, CZA demonstrated a better clinical cure and less common acute kidney damage than colistin when used to treat infections due to CPE.[12] In 2021, Tootla et al.[13] were the first to report a SA case wherein a child with persistent CRE *Serratia marcescens* was successfully treated using CZA. The authors voiced their concern that if additional antimicrobial stewardship interventions do not accompany the

initiation of therapy with these new antibiotics, the longevity of these drugs will be jeopardised.[11] The overuse of antimicrobials is one factor that has led to the development of resistance.[14]

The lack of surveillance systems is another contributing factor towards the development of AMR.[15] Morel et al.[16] reported on a study to determine the requirements of antimicrobial surveillance for new drugs. The authors reported on the shortfall of current antibiotic surveillance systems in that they only monitor drugs that have been on the market for a long time.[16] A new public system should be initiated that is focused on detecting the emergence of resistance to new antibiotics.[16] SA already has a system to monitor antibiotic resistance via the National Institute for Communicable Diseases (NICD). However, as reflected in their most recent report, CZA is not yet part of the antibiotics under their surveillance.[17]

CZA represents a good treatment option for OXA-48 CPE.[18] However, its uncontrolled use in treatment could be disastrous for its future preservation as a therapeutic option.[11] The country already seems to be witnessing a rise in resistance to CZA due to its increased use in the private sector.[11] Brink et al.[11] noted the need for appropriate and effective initial therapy while promoting antibiotic stewardship. In 2022, utilisation data already indicated a sharp increase in the annual growth rate of CZA consumption over the previous three years.[11]

If these drugs are to be preserved, withholding their use from resistant infections that can be treated with currently available antibiotics is a vital part of stewardship.[11] Furthermore, hospitals should continue to adhere to all their protocols and antimicrobial stewardship interventions when introducing these drugs into their prescription lists.[11] Infection prevention and control (IPC) is also upheld as one of the most cost-effective interventions against AMR.[19]

Limitations and recommendations

The testing period for this study was not long enough to establish a proper trend confidently. We recommend further surveillance to understand better how in vitro OXA-48 isolates respond to this drug in SA.

Conclusion

There was a rise in OXA-48 resistance to the CZA drug between 2020 and 2021. Surveillance and stewardship measures are critical to ensure that the drug does not lose its effectiveness in the country's health system. Further surveillance studies for CZA susceptibility in SA, such as prolonging the surveillance period by another year or two, would give a clearer picture of the possible trend for resistance and how this problem could be curbed.

Conflict of interest

None.

Funding source

None.

Ethical approval

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