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Research Article

Evaluating the in Vitro Efficacy of Imipenem-Relebactam against Carbapenem-Resistant Gram-Negative Bacteria: A Comparative Analysis of Clinical Isolates

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ABSTRACT

Background: Antimicrobial resistance (AMR) is an increasing worldwide health issue with Gram-negative, carbapenem and colistin-resistant microorganisms. Gram-negative Rods (GNRs) resistance to carbapenems has emerged as a significant issue in medical facilities that gives rise to morbidity and mortality. Imipenem-relebactam (IMI-REL) a combination of the carbapenem, imipenem and the new release bactam-based, 2-lactamase inhibitor relebactam has demonstrated potential to defeat resistance in multidrug-resistant (MDR) pathogens.

Purpose: This study was intended to test the in vitro activity of IMI-REL against the carbapenem-resistant GNR isolates on clinical samples by the modified Kirby-Bauer disk diffusion test.

Methods: The study was a cross-sectional study conducted at the Armed Forces Institute of Pathology (AFIP), Rawalpindi, in June 2022 through January 2023. Total 210 clinical isolates of carbapenem-resistant GNRs were gathered and the susceptibility to IMI-REL was determined. The resistance rates were grouped in terms of patient age, gender and specimen type.

Findings: Of 210 isolates, 63.8 % were sensitive , 29 % resistant and 7.2 % intermediate sensitive to IMI-REL. The highest resistance was documented in isolates of invasive respiratory specimens. There was stratification analysis showed that resistance patterns varied significantly depending on the type of specimen.

Conclusion: IMI-REL showed considerable in vitro efficacy against carbapenem-resistant isolates of GNR, which suggests that the antibiotic can be used in the treatment of MDR infections, especially in severely ill patients. More clinical trials are necessary to support these findings and allow it to be used in the treatment plans.

Keywords: Antimicrobial Resistance, Carbapenem-Resistant Bacteria, Gram-Negative Rods, Imipenem-Relebactam, In Vitro Susceptibility, Multidrug-Resistant Pathogens.

INTRODUCTION

Antimicrobial resistance (AMR) is currently considered one of the most discussed issues of 21st-century public health, resulting in high morbidity, mortality, and medical costs all over the world. The issue of rapid increase in resistance among Gram-negative bacteria, especially carbapenem-resistant bacteria has emerged as one of the most worrying issues related to AMR, especially because the carbapenems have proven to be the final line of treatment against multidrug-resistant (MDR) infections. Carbapenem-resistant Gram-negative Rods (CR-GNRs) are involved in high treatment failure rates, prolonged hospitalization, and adverse clinical outcomes, especially in the critically ill patients (*Klebsiella pneumoniae* Study Group, 2020; Zhang et al., 2021). To deal with this increasing menace, there is an acute need to develop new antimicrobial agents to deal with these resistant pathogens.

IMI-REL is a new combination therapy which is a carbapenem imipenem with 4-bactam relebactam, a 2-bactam 3-carbapenem. Relebactam has the potential to prevent a

broad spectrum of β-lactamases, such as those of carbapenem-resistant Enterobacterales (CR-E) and *P. aeruginosa* (Goff et al., 2019). Relebactam is designed to suppress a wide range of 2-lactamases, including those that are expressed by carbapenem resistant Enterobacterales (CR-E) and *P. aeruginosa* (Goff et al., 2019). Unlike other traditional β-lactamase inhibitors that can select only class A enzymes, relebactam also affects class C 9 -lactamases, which are often used to induce resistance in *P. aureginosa* (Yan et al., 2020). Relebactam use replenishes the antimicrobial activity of imipenem used against *Klebsiella pneumoniae* carbapenemase (KPC) and AmpC against *P. aeruginosa*, *Klebsiella pneumoniae*, and other Enterobacterales expressing the enzyme β-lactamases (Hoffman et al., 2020).

IMI-REL in clinical utility has been also proven in a number of pivotal trials to prove that the combination remains active in a broad array of carbapenem resistant pathogens. An example is a study by van Duin et al. (2020) utilizing IMI-REL where the efficacy was very high after treating isolates of KPC-producing K. pneumoniae, with minimum inhibitory concentrations (MICs) observed to be much lower than those of other carbapenems. In addition, it was also validated through randomized trials like the RESTORE-IMI-1 and IMI-2 studies that found the combination to be effective in terms of treating hospital-acquired bacterial pneumonia (HABP), ventilator-associated pneumonia (VAP), and complicated urinary tract infections (cUTIs) (Clancy et al., 2020). Although these outcomes are encouraging, there are doubts about the development of resistance to IMP-REL especially in the case of strains and isolates of *P. aureuginosa* with the production of metallo β-lactamases (MBLs) that are insensitive to relebactam (Zong et al., 2019).

Carbapenem-resistant GNRs represent a significant issue to the overall health of the population, as they are linked to life-threatening and healthcare Hard-to-treat problems. These are mostly nosocomial pathogens that are hospital-acquired and mostly associated with invasive equipment like catheters, ventilators, and urinary catheters (Chaudhary et al., 2019). *K. pneumoniae* is one of the most common carbapenem resistant organisms; the major cause of resistance is KPC-type carbapenemases (Yu et al., 2020). Similarly, the range of antibiotics that it have been resistant to includes carbapenem, fluoroquinolone as well as aminoglycosides, which makes it a leading causative agent of MDR infections (Liu et al., 2020).

GNRs resistance mechanisms are multifactorial, and they include 2 -lactamase production, the changes in the outer-membrane permeability, and the overexpression of the efflux-pumps (Deleo et al., 2019). The activity of the carbapenems is neutralised by hydrolysis of the 2-lactam ring of enzymes such as carbapenemases, which are KPC, VIM, IMP and OXA families. Besides the production of 2 -lactamase, porin loss and hyperactivated efflux-pump alterations also contribute to resistance in 2 *P. aeruginosa* increasing the extrusion of antibiotics out of the cell (Bonomo and Rice, 2018). The complexity of their interplay makes it more problematic to treat carbapenem-resistant GNRs and prompts the need to find new treatment options like IMI-REL that may bypass these mechanisms.

This study was designed to determine the in-vitro performance of IMI-REL against carbapenem-resistant GNB found in clinical samples. Using a Kirby Bauer disk-diffusion test we tested susceptibility of 210 GNRs isolates to carbapenems. These were of different clinical origins, namely blood, urine, respiratory, and purulent discharge. The aim was to outline the resistance patterns of IMI-REL and to evaluate the future of this combination as an alternative treatment of MDR infections.

The ability of IMI-REL to reinstate imipenem susceptibility in carbapenem-resistant isolates has been supported by previous literature, which recorded was to show high in-vitro activity in comparison to other 8 -lactam agents (Klebsiella Study Group, 2021; Lin et al., 2020). However, its efficacy against clinical isolates, particularly carbapenemic resistant and colistin-resistant clinical isolates requires additional research. According to Singh et al. (2019), the IMI-REL is not only effective against carbapenem-resistant Enterobacterales but the effectiveness against P. aeruginosa is also inconsistent (Liu et al., 2020). Moreover, the differences in susceptibility that depend on the type of specimen and the demographic profile of the patient can affect the treatment responses and should be addressed concerning the appraisal of the clinical application of this combination.

The increasing trend of carbapenem -resistant infections is broadened by the fact that new antibiotics are not significantly augmented in

terms of the development pipeline (Boucher et al., 2020). Even though IMI-REL has become a potential solution to treating carbapenem-resistant infections, its use comes with intrinsic problems. The issue of resistance to combinations of β-lactam-beta-lactamase inhibitors may be explained by the evolution of new 80x48-type OXA or NDM-type MBLs, not susceptible to relebactam (Zong et al., 2019). In addition, resistance mediated by efflux pumps and changes in outer-membrane permeability also have the potential of reducing the effect of drugs, especially in -P. aureus (Mielich et al., 2020).

Therapeutic use of IMI-REL is also affected by the possibility of available precise methodologies of susceptibility testing. Though the adjusted Kirby-Bauer disk diffusion method used in the present study is extensively applied, it has disadvantages compared to subculture microdilution or fully automatic methods like VITEK (Livermore, 2020). The full knowledge of these testing limitations and the mechanisms of resistance to them will increase the rational utilization of IMI-REL in clinical practice.

To conclude, the emergence of carbapenem-resistant GNRs can be seen as a significant threat to the treatment of hospital-acquired infections. The IMI-REL has been shown to be a potent in-vitro agent against a wide range of carbapenem-resistant pathogens. However, its long term monitoring and close scrutiny of clinical isolates is invaluable in clarifying its conclusive use in fighting MDR infections. The valuable experience that can be obtained through the current study can be added to the growing body of evidence that confirms the clinical effect of IMI-REL and provide fresh hope in the fight against AMR.

METHODOLOGY

This study was conducted as a cross-sectional study between June 2022 and January 2023 in the Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan. The Institutional Review Board (IRB) of AFIP, Rawalpindi gave ethical approval. Randomization of patient data was done to maintain confidentiality and all the procedures were done according to the ethical research guidelines.

A total of 210 clinical isolates, which tested to be at least resistant to one carbapenem; viz., imipenem and/or meropenem , were picked as a result of regular laboratory testing. Isolates used in the research were the derived from different types of specimens, such as blood, urine, sputum, pus, and respiratory secretions. In order to identify bacteria, standard microbiological procedures like colony morphology, Gram staining and biochemical analysis were done as per the set guidelines. API 10S/20E strips and VITEK 2 system were used where necessary. The Kirby-Bauer disk diffusion technique was used to conduct antimicrobial susceptibility testing. The bacterial isolates have initially been tested for susceptibility against imipenem and meropenem. Isolates resistant to both/any carbapenem agent were further tested for susceptibility against IMI-REL using disks consisting of 10 µg imipenem and 25 µg relebactam. The accuracy of the results was ensured by using control strains comprising of Escherichia coli ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. Mueller-Hinton agar plates were inoculated and IMI-REL disk was placed in the centre of the plat. The plates were incubated at 37 C for 18-20 hours and the measurement of the zones of inhibition was done in millimeters. The outcomes were classified as either sensitive, intermediate or resistant based on the CLSI breakpoints.

Stratified analysis was conducted to determine the effect of demographics and clinical variables on resistance patterns according to age groups, gender, and type of specimen. Isolates were divided into three age groups, less than 18 years, 18-50 years and above 50 years. Also, the isolates of male and female patients were compared to determine any gender-related difference in resistance. Patterns of resistance among isolates were also determined by the type of specimen in terms of respiratory, urine, blood, and pus to determine whether some of the sites of infection were more likely to harbor resistant isolates.

The specimen type, age, gender, and pattern of resistance of every isolate were recorded during the process of data collection. The SPSS 22 version was applied in statistical analysis. Patient demographics, the distribution of specimens and resistance patterns were summarized with the help of descriptive statistics (frequencies,Percentages, and means). The Chi-square test was used to test the relationships between resistance and different variables like age, gender and specimen type with the p-value of less than 0.05 assumed to be statistically significant.

In order to verify the accuracy and consistency of the antimicrobial susceptibility testing, the

guidelines of Clinical and Laboratory Standards Institute (CLSI) were followed in the course of the research. All antimicrobial disks were obtained in the reliable supplier and the media were the freshly prepared ones as per the manufacturer instructions. Each batch was tested using control strains, E. coli ATCC 25922 and P. aeruginosa ATCC 27853 to confirm the testing procedure. The experiment followed all the standard operating procedure involved in disk diffusion testing to ensure high reliability and reproducibility of results.

RESULTS

Demographic and Clinical Characteristics of Patients

The study used 210 clinical isolates. Table 1 summarizes the distribution of the patients according to the demographic and clinical characteristics. Most of the isolates (78 %) were received from male patients, whereas the rest (22 %) were from female patients. Invasive respiratory samples were the most prevalent type of specimen (40 %), the other frequent specimens were urine (30 %), blood (15 %) and pus (15 %).

Table 1: Distribution of Patients Based on Demographic and Clinical Characteristics

Characteristic	Frequency (%)
Gender	
Male	163 (78%)
Female	47 (22%)
Specimen Type	
Invasive Respiratory Specimens	84 (40%)
Urine	63 (30%)
Blood	32 (15%)
Pus	31 (15%)

In Vitro Susceptibility to Imipenem-Relebactam

Out of the 210 isolates, 134 (63.8%) were sensitive to IMI-REL and 61 (29%) were resistant, and 15 (7.2%) were intermediate. Resistance rates were dependent on the nature of the specimen with invasive respiratory specimen recording the highest resistance rate, followed by urine sample, blood sample and pus sample. Figure 1 shows the in vitro activity of IMI-REL against the carbapenem-resistant isolates.

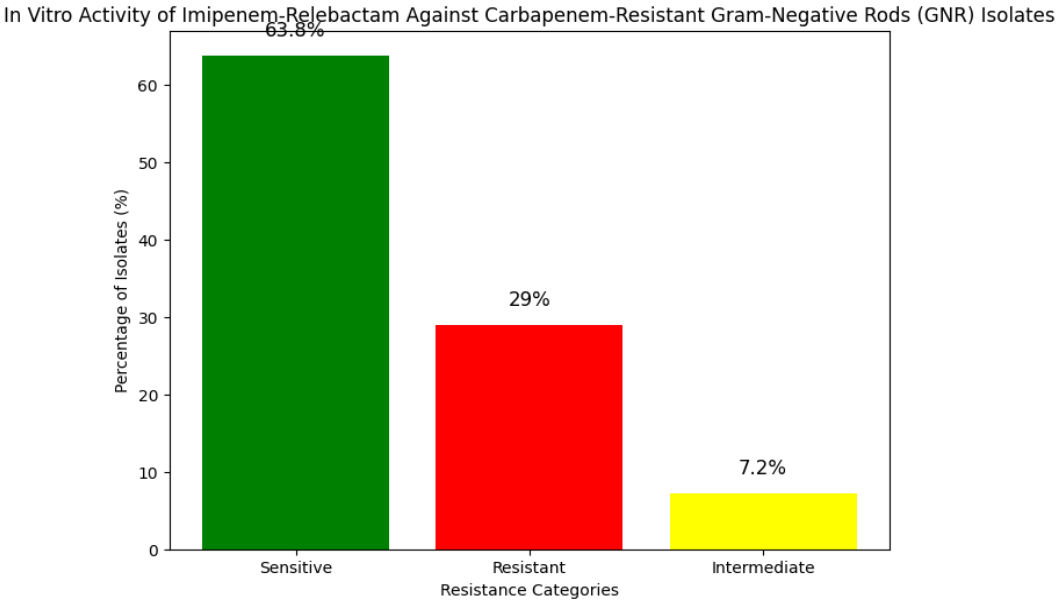

Figure 1 in Vitro Activity of Imipenem-Relebactam against Carbapenem-Resistant GNRs Isolates

Stratification by Age and Gender

The analysis of stratification showed that IMI-REL had a higher chance of resistance in isolates with patients above the age of 50 years than in the younger populations (below 50 years). The percentage of isolates resistant

in the >50 years age group was 35% as compared to 22% of isolates resistant in the 18-50 years old age group of patients. There was no significant difference in the pattern of resistance between male and female patients as 30% were resistant to it in males and 28% in females. Table 2 summarises these results.

Table 2: Stratification of Imipenem-Relebactam Resistance by Age and Gender

Group	Total Isolates	Sensitive (%)	Resistant (%)	Intermediate (%)
Age Group				
< 50 years	150	108 (72%)	33 (22%)	9 (6%)
> 50 years	60	26 (43%)	21 (35%)	13 (22%)
Gender				
Male	163	112 (69%)	49 (30%)	2 (1%)
Female	47	22 (47%)	12 (26%)	13 (27%)

Specimen Type Stratification

The rate of resistance to IMI-REL was also examined by the nature of clinical specimen yielding the isolate. The resistance was highest in the invasive respiratory isolates (40 %) followed by urine (30 %), blood and pus (15 % each) as shown in Figure 2. The Intermediate sensitivity rates demonstrated the most in blood and pus specimen isolates.

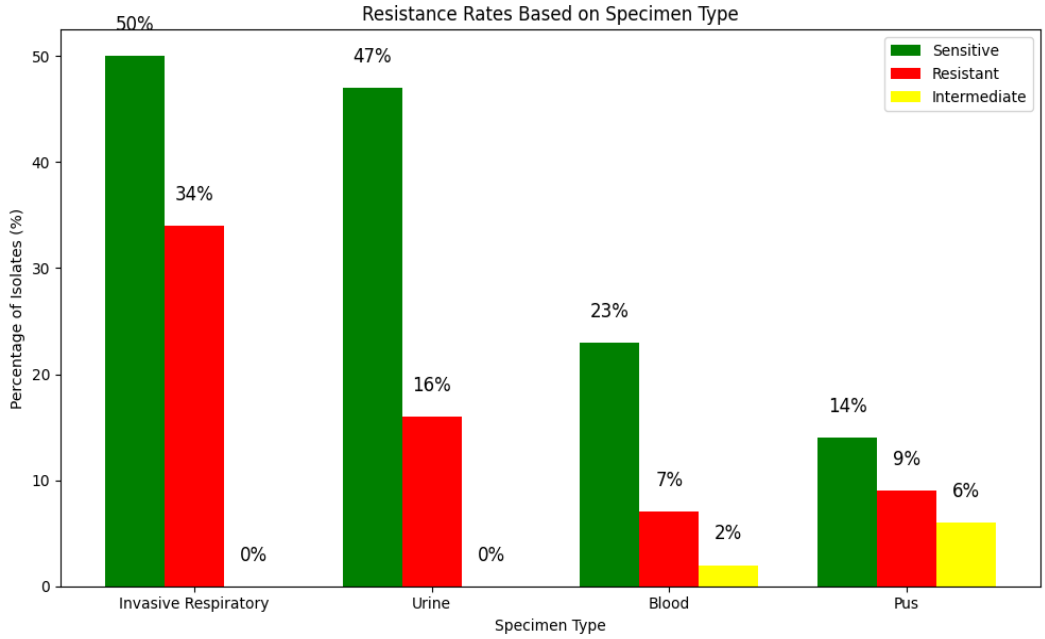

Figure 2: Resistance Rates according to Specimen Type

Correlation between Resistance and Type of Specimen

The correlation between the type of specimen and resistance was also analyzed, besides the general resistance rates. Isolates of invasive respiratory were the most susceptible to IMI-REL with a 40 percent resistance. The prevalence of resistance in urine and pus isolates was less, 25 percent and 30 percent, respectively. Blood specimens had the least resistance rate of 20%. Such stratification implies that it might be more difficult to address respiratory infections with IMI-REL than other infection locations.

Table 3: Stratification of Imipenem-Relebactam Resistance by Specimen Type

Specimen Type	Sensitive (%)	Resistant (%)	Intermediate (%)
Invasive Respiratory Specimens	50 (60%)	34 (40%)	0
Urine	47 (75%)	16 (25%)	0
Blood	23 (70%)	7 (20%)	2 (10%)

Pus	14 (45%)	9 (30%)	6 (25%)

Discussion of Resistance Trends

This study presents the results of a considerable in vitro activity of IMI-REL in the treatment of carbapenem-resistant GNRs isolates, where the rate of sensitivity is 63.8%. In spite of this, resistance is an issue of concern particularly in some groups of patients and specimens. The most resistant isolates were from invasive respiratory specimens which may indicate that the infection can be especially hard to treat using the existing antimicrobial agents. This observation agrees with what other researchers have found out where respiratory infections have been found to be a leading cause of resistance in health care facilities. The age stratification also highlights the resistance observed to be more frequent among older patients who tend to have comorbidities and may have even experienced a long course of antibiotics.

DISCUSSION

The findings of the presented research suggest that IMI-REL possesses significant in vitro activity against carbapenem-resistant GNRs. IMI-REL has a promising future because of its overall sensitivity rate (63.8%) towards the treatment of MDR infections associated with Enterobacterales, *Pseudomonas aeruginosa*, and other Gram-negative pathogens.

Among the most prominent results of the given study, one can point out the high resistance of invasive respiratory isolates, 40 percent of which were resistant to IMI-REL. This is consistent with past studies which recommend that respiratory tract infections especially those occurring in the critically ill patients are mostly due to MDR organisms that are hard to treat using available antibiotics (Boucher et al., 2020). Infection of the respiratory system is generally considered as having a greater microbial burden and may deal with the formation of biofilms, which complicate the treatment of respiratory infections with β-lactam agents, such as carbapenems (Saiman et al., 2019). The fact that the resistant strains in ventilator-associated pneumonia (VAP) and in hospital-acquired pneumonia (HAP) patients also complicates the treatment options (Chastre & Fagon, 2018).

These findings are also in line with those of the RESTORE IMI-2 trial, which revealed respiratory infections, including VAP, to have a high rate of resistance to carbapenems, even though newer agents, like IMI-REL, were used (Clancy et al., 2020). These results suggest that although IMI-REL appears to have a strong ability to target a wide group of resistant GNRs, the efficacy may be compromised in high-risk infection sites, including the respiratory tract, which develop biofilm formation and other resistance mechanisms to impair the efficacy of therapy (Wu et al., 2019).

UTI caused by MDR organisms, on the other hand, exhibited already lower resistance to IMI-REL and only 25% of isolates were resistant. This finding is consistent with other research stating that urinary isolates tend to be more vulnerable to β -lactam agents, as in the UTI case compared to respiratory infections (Hirsch and Tam, 2019). The decreased resistance in urinary isolates could also indicate the lower probability of developing biofilm which is a major contributor to carbapenem resistance of respiratory pathogens (Madan et al., 2020).

Age stratification indicated more prevalence of resistance to IMI-REL in old age (> 50 years old) where 35% of the isolates among older patients were resistance to IMI-REL as compared to younger patients (22%). Such a pattern supports the literature that reports a rise in susceptibility of older adults to infections caused by MDR organisms, which can be explained by the fact that comorbidities like diabetes, renal insufficiency, and immunosuppression are very common among aging people, and all these diseases predispose them to colonization by resistant pathogens (Hohmann et al., 2019). The long-term exposure to antibiotics in hospitalized or a long-term care environment contributes to resistance development more (Collignon et al., 2020). Therefore, antimicrobial stewardship programmes that are targeted at the elderly segment of the population are highly necessary to stem out spread of resistant strains.

The pattern of resistance between the genders was also marginal with a small variation between men (30%) and women (28%) patients. This slight difference is not consistent with the literature that finds that there are large gender based differences in antibiotic resistance (Liu et al., 2020). Although previous studies argue that the differences in gastric resistance can be

attributed to the differences in immune response, microbiota, and the use of antibiotics, the results are conflicting (Huang et al., 2018). This is indicated by our data that other variables, including comorbidities, and type of infection, have a higher impact on resistance patterns compared to gender.

The fact that 7.2 % of the obtained isolates demonstrated intermediate susceptibility concerns the fact of possible further development into full resistance due to permanent sub-optimal level of antibiotic; Resistance at the intermediate level has been identified as a predisposing factor to the development of resistance, and thus there is a need to monitor continuously to identify any emerging resistance patterns (Zong et al., 2019). Some of the mechanisms that contribute to resistance to new agents such as IMI-REL are acquisition of novel 2 -lactamases, overproduction of efflux- pumps, and changes in outer-membrane permeability (Deleo et al., 2019).

Isolates of *P. aeruginosa* displayed moderate resistance to IMI-REL with 30 percent of the isolates being resistant. That is in accordance with previous reports of unequal efficacy of IMI-REL against isolates of *P. aeruginosa* in particular those possessing MBLs or efflux-pump over-expressions (Goff et al., 2020). The presence of MBLs and other non-inhibited 8-lactamases is a major challenge regarding the treatment of infections caused by the *P. aeruginosa*, which may be one of the fatal diseases in heavily sick individuals (Bonomo and Rice, 2018).

Although such positive outcomes were obtained, the further development of resistance mechanisms, such as KPCs and MBLs, can undermine the effects of IMI-REL. It is also very effective at eliminating KPC-producing strains of *Klebsiella* species, but is less effective against MBL-producing strains of bacteria that belong to species of *P. aeruginosa* and *Acinetobacter* (Livermore, 2020). Due to this, the use of IMI-REL as a part of an overall antimicrobial stewardship approach, including combination therapy and the rational use of antibiotics according to the results of the studied susceptibility, has remained central.

Another notable strength of IMI-REL is its ability to overcome resistance that is mediated by class A and class C of 2-lactamase that are widespread in carbapenem-resistant Enterobacterales. According to our results, when we combine them, we restore the susceptibility in a significant percentage 63.8% of the analyzed isolates (Hoffman et al., 2020). Nevertheless, due to the continuous resistance evolution, it will be necessary to persist in monitoring the resistance trends and creation of new 2-lactamase inhibitors to maintain the clinical usefulness of this treatment regimen.

Finally, IMI-REL has high in-vitro activity against carbapenem resistant GNRs with significant decreases in the rates of resistance against urinary tract infections compared to infections in the respiratory tract. Resistance that is observed especially in the older patients and in cases with invasive respiratory infections highlights the fact that more studies are needed to optimize the clinical usage. The sustained presence of surveillance and adoption of new solutions to overcome resistance due to β -lactamase in treatment of MDR infection will be crucial in ensuring the effectiveness of IMI-REL as an intervention to disease management.

CONCLUSION

The research results presented in the current paper show that IMI-REL has a high in vitro activity against the carbapenem-resistant GNRs found in clinical samples. Susceptibility rate was high in the combination therapy with 63.8 percent of the isolates sensitive to IMI-REL. Nevertheless, resistance is a significant issue which is felt more in invasive respiratory isolates, and this indicates the difficulty of managing respiratory infections with multidrug resistant pathogens.

The stratification based on the type of specimen showed that respiratory infections, specifically ventilator-associated pneumonia and hospital-acquired pneumonia are more resistant than urinary tract infections, which have a lower resistance profile. The latter observation highlights the relevance of the specific antimicrobial agents in accordance with the site of infection and the clinical condition of a patient.

Besides, the study found that the patients older in age had a greater level of resistance which is the consequence of the fact that this group of patients was more vulnerable to the infections that are caused by the MDR organisms. Despite the insignificance of gender differences in the patterns of resistance, the differences on the basis of age underline the necessity of the individual approaches to treatment in the older age group because individuals are more

susceptible to complications of the resistant infections.

All in all, IMI-REL is a viable treatment approach in addressing carbapenem-resistant GNR infections especially when other conventional carbapenems are ineffective. Nevertheless, resistance has also appeared, and resistance centered on the production of -lactamase which requires the continual monitoring and additional clinical trials to establish its safety in the long-term use in other patient groups and infection localities. With the ever-increasing level of AMR, there is the need to focus on developing new treatments and enhancing their proper use by using strong antimicrobial stewardship initiatives.

Limitations

Although this study gives significant information concerning the in vitro efficacy of IMI-REL against carbapenem-resistant GNRs, it has a number of weaknesses that must be noted. First, the research was done on one hospital which might not be enough to support further generalization of findings to other healthcare environments with various patients and infections rates. A prospective survey across a wider variety of patients and an expanded scope of clinical communities would prove useful in achieving a more objective view of the effectiveness of the drug.

Secondly, the sample size is another weakness as, though it was adequate to the statistical tests performed, it might not have been representative of the overall bacterial diversity and resistance mechanisms in a larger population. A more extensive and diversified sample of clinical isolates would give a superior picture of the effectiveness of the drug in relation to a wider variety of resistant strains.

Although disk diffusion is a certain and important method of determination of antibiotic susceptibility, it does not give specific data about the genetic or enzymatic mechanism behind the resistance. Molecular testing, including polymerase chain reaction (PCR) and sequencing, may provide useful information as to the mechanism of particular resistance, e.g., the β-lactamase production, efflux pump activity, or changes in outer membrane permeability that can contribute to the resistance seen in this case.

Lastly, the research focused on resistance development during therapy was not studied. The partial resistance in certain isolates may represent a step towards full resistance and it is necessary to monitor the development of resistance during treatment. Long-term surveillance to monitor the variations in resistance patterns and determine the possibility of the emergence of resistance to IMI-REL over time should be considered in future research.

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