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The Clinical Efficacy of Adding Ceftazidime/Avibactam to Standard Therapy in Treating Infections Caused by Carbapenem-Resistant *Klebsiella pneumonia* with blaOXA-48-like Genes

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Al MAAMON R.T. ABU JABER
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Al MAAMON T.R. ABU JABER

Abstract

The Clinical Efficacy of Adding Ceftazidime/Avibactam to Standard Therapy in Treating Infections Caused by Carbapenem-Resistant *Klebsiella pneumonia* with blaOXA-48-like Genes

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The FDA has approved ceftazidime/avibactam (CAZ-AVI) for the treatment of infections brought on by resistant gram-negative bacilli, especially illnesses brought on by Enterobacterales bacteria that are resistant to carbapenem. There is currently a dearth of clinical evidence, especially from Saudi Arabia. This study, a retrospective cohort study, compared the clinical and microbiological outcomes of patients treated with CAZ-AVI as monotherapy and as an adjuvant to standard therapy for carbapenem-resistant Klebsiella pneumonia (CRKP) OXA-48 infections to those treated with standard medications at the Armed Forces Hospital in the southern region of Saudi Arabia. Patients with infections similar to CRKP OXA-48 who received antibiotics for longer than seven days between August 1, 2018, and May 5, 2023, were included in the study. From the clinical records, baseline demographics and clinical/microbiology efficiencies of the patients were extracted and evaluated in accordance with the relevant definitions. The possible independent variable for CAZ-AVI efficiency was found using univariate and multivariate logistic regressions. For the assessment, 114 patient files in total were present. Of these patients, 64 were part of the intervention group (using CAZ-AVI in addition to regular therapy), while 50 were part of the comparison group (using standard therapy). After analysis, the clinical success rate of CAZ-AVI was 42.2% ($p = 0.028$). The intervention group exhibited significantly higher rates of microbial eradication (68.8% versus 42.0%; $p = 0.007$), as well as decreased 30-day all-cause mortality (50.0% versus 70.0%; $p = 0.036$) and infection recurrence (7.8% versus 24.0%; $p = 0.019$). Clinical and microbiological outcomes were statistically significantly better with CAZ-AVI add-on therapy than with monotherapy. Additionally, as independent negative predictors, sex (female percentage), ICU hospitalization, and fever were negatively correlated with patients' 30-day all-cause mortality. The only variables that significantly influenced the clinical efficacy of the CAZ-AVI were fever, CRP bio levels, inotropes, and ICU hospitalizations. WBC counts and fever episodes were negative predictors of CAZ-AVI's ability to eradicate microorganisms, but the length of CAZ-AVI therapy had a beneficial effect. This study demonstrates how well CAZ-AVI works against infections that resemble CRKP OXA-48. To ensure optimal survival

and efficacy, doctors should individualize the CAZ-AVI dose depending on co-existing risk factors, as suggested by the influencing independent variables illustrated above.

It is advised to conduct prospective multicenter, randomized control trials and to use customized CAZ-AVI precision administration according to the unique needs of each patient.

Key Words: ***carbapenem*** resistance, Klebsiella pneumonia, OXA-48-like genes, ceftazidime/avibactam, clinical efficiency

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Abbreviations

AmpC	Ampicillin resistant gene group C (Cephalosporinase)
AMR	Antimicrobial resistant
ARB	Antibiotic resistant bacteria
ARG	Antibiotic resistant gene
ATM	Azithromycin
CAZ-AVI	Ceftazidime Avibactam
CBC	Complete blood count
CDC	Center for disease control and prevention
CPE	Carbapenemase producing Enterobacterales or Enterobacteriaceae
CRE	Carbapenem resistance Enterobacteriaceae or Enterobacteral
CRP	C- reactive protein
CRPK	Carbapenem resistant Klebsiella pneumonia
CSPK	Carbapenem susceptible pneumonia Klebsiella
CTX M	Cefotaximase enzyme
ESBL	extended spectrum beta lactamase
FDA	Food and drug administration
GES	Guiana extended spectrum
GNB	Gram negative Bacteria
IMI	Imipenem resistant
IMP	Imipenemase (metallo-B- lactamase)
KPC	Klebsiella pneumoniae carbapenemase
MBLs	Metallo-B-lactamases
MER-VAB	Meropenem/Vaborbactam
MGEs	Mobile genetic elements
NDM	New Delhi metallo-B-lactamase
NMC-A	non-metallo carbapenemase-A
OmpK	Outer membrane porins
OXA	48 oxacillinase 48
PCT	Procalcitonin
PMB	Polymyxin B
SFC	Serratia fonticola carbapenemase
SHV	sulphydryl variable
SME	Serratia marcescens enzyme
ST	Multilocus sequence type
VIM	Verona integron-encoded Metallo-B-lactamase
WHO	World health organization

CHAPTER I

Introduction

1.1 Background of the study

Numerous ailments related to healthcare, such as meningitis, bloodstream infections, wound or surgical site infections, and pneumonia, can be caused by the gram-negative bacterium Enterobacterales. Worldwide, the frequency of instances of bacteremia due to Enterobacterales has increased, especially when resistant strains of Klebsiella pneumonia are involved (ECDC, 2018). K. pneumoniae bacteria are becoming more resistant to antibiotics; this has happened most recently to the carbapenem antibiotic class (Paczosa and Mecsas, 2016). Regretfully, carbapenem medications are usually the last choice for treating gram-negative infections that are resistant to other antibiotics (Paczosa and Mecsas, 2016). Antibiotics such as carbapenem are commonly used to treat infections caused by Enterobacterales because these bacteria produce extended-spectrum beta-lactamase (ESBL), which is a common cause of infections (Lee et al., 2016). However, the rise of isolates resistant to carbapenem has been caused by the misuse or inappropriate handling of these antibiotics.

Human health is seriously threatened by antibiotic resistance, which is a growing problem. It is estimated that by the year 2050, antibiotic-resistant infections will lead to 10 million deaths yearly (Band et al., 2018). Because of the high rates of antibiotic resistance, the lack of therapeutic choices, and the changeable optimal treatment duration, it is difficult to manage infections caused by carbapenem-resistant K. pneumonia (CRKP) (Zhang et al., 2018; Chen et al., 2021). K. pneumonia cause of hospital- acquired infections and community-acquired infections. So, it is classified by the World Health Organization as a critical priority antibiotic-resistant bacteria (WHO, 2017). Clinical, agricultural, and urban settings are all suffering from an increase in carbapenem resistance rates (Walsh et al., 2011; Munoz-Price et al., 2013; Wang et al., 2017; Kazi et al., 2015; Albiger et al., 2015; Singh-Moodley and Perovic, 2016). Patients infected with susceptible K. pneumonia bacteria have a mortality rate of 34%, while patients infected with CRKP have a mortality rate between 30% and 44%, and about 70% in cases of bacteremia (Hoxha et al., 2016; Akturk et al., 2016; Podschun and Ullmann, 1998; Borer et al., 2009; Ben-David et al., 2012). According to the Centers for Disease Control and Prevention and the China Antimicrobial Surveillance Network, most of carbapenem-resistant Enterobacterales are carbapenem-resistant K. pneumonia and most of these infections are lower respiratory infections, (Hu et al., 2016; Kadri, 2020). Interestingly, CRKP is linked to

a higher death rate—roughly two times higher mortality than enterobacterial infections responsive to carbapenem (Kadri, 2020; Rodríguez et al., 2021).

According to numerous reports, the CRKP's basic mechanism of carbapenem resistance is the synthesis of carbapenemases enzymes (Wang et al., 2020). Serine-β-lactamases with Ambler sub-classes (A and D) and metallo-β-lactamases with Ambler sub-classes (B) are the two groups of Enterobacterales carbapenemases that are clinically important (Walsh et al., 2008). Several chromosomal genes (BIC-1, FPH-1, NmcA, PenA, SFC-1, SHV-38, and SME) or plasmids (FRI-1, GES, and KPC) are the source of genetically encoded class A carbapenemases. KPC strains have been strongly linked to CRKP (Queenan and Bush, 2007). However, class D carbapenemases, which are encoded by OXA-48 and have eleven known variants (OXA-48-like) that show pertinent geographical differences, were shown to be widely distributed throughout Enterobacterales, including K. pneumonia (Logan and Weinstein, 2017; Pitout et al., 2015). These OXA-48 strains have been regularly reported in nosocomial outbreaks worldwide, especially in the Mediterranean region, since the identification of OXA-48 carbapenemase in Turkey in 2004 (van Duin and Doi, 2017).

In general, currently available penicillin, cephalosporins, and carbapenems have little in vitro efficacy against this resistant bacterium or CRKP bloodstream infections (Neuner et al., 2011). Combining ceftazidime, a third-generation cephalosporin, with avibactam, a non-β-lactam/lactamase suicidal inhibitor, has shown microbiological and clinical efficacy against K. pneumonia carbapenemases in class A, C, and a few class D (OXA-48), but not class B metallo-β-lactamases (Shields et al., 2017). The US-FDA, EMA, and Chinese-FDA have all approved CAZ-AVI for the treatment of complex urinary tract (including pyelonephritis), intra-abdominal, and hospital-acquired pneumonia infections (Chen et al., 2021). There is growing evidence that CAZ-AVI can be used to treat infections caused by resistant gram-negative bacteria, notably carbapenem-resistant Enterobacterales infections (Krapp et al., 2017; Tumbarello et al., 2019; Castón et al., 2017; van Duin and Bonomo, 2016; Gu et al., 2021). Systematic reviews provided clinical evidence for the efficacy of CAZ-AVI in hospitalized patients with multidrug-resistant K. pneumonia and carbapenem-resistant Enterobacterales (Soriano et al., 2021; Zhen et al., 2022). Real-world investigations showed that this novel β-lactam/lactamase inhibitor combination is the best therapeutic option for CRKP because it reduced 30-day mortality in bacteremia, carbapenem-resistant Enterobacterales-associated clinical failure, and 14-day microbiological failure rates (Gu et al., 2021; Mazuski et al., 2021; Zheng et al., 2022). CAZ-AVI treated alone or in combination with aztreonam has recently been shown to have good antibacterial and synergistic

bacteriostatic/bactericidal actions against microorganisms generating KPC, IMP, OXA, and/or NDMI (Lu et al., 2022).

Despite the promising efficacy of CAZ-AVI in carbapenem-resistant Enterobacterales and CRKP infections, clinical experience is currently limited, and more real-world research is required. Carbapenemases are widespread in K. pneumonia isolates in Saudi Arabia, with findings indicating that OXA-48 is the most common carbapenemase, followed by the New Delhi metallo-lactamase (Alotaibi, 2019; Hakeam et al., 2021). There is still a dearth of studies comparing the outcomes of patients in Saudi Arabia with carbapenem-resistant Enterobacterales (CRE) infections treated with CAZ-AVI vs other regimens. The present study aimed to investigate the clinical and microbiological efficacy of CAZ-AVI, as well as the mortality rates of patients with CRKP OXA-48-like infections, by comparing the treaments outcomes in the patients treated with CAZ-AVI as monotherapy or as an add-on to standard therapy to those who received other antibiotics.

1.2 Statement of the Problem

Multidrug-resistant Neisseria gonorrhoea, carbapenem-resistant Enterobacteriaceae (CRE), and Clostridium difficile are the three types of bacteria that pose the greatest threat to human health globally (Zowwai et al., 2015). Over the last years, infections caused by CRE bacteria has been distributed worldwide. These patients have a high mortality rate (Normann et al., 2011).

According to global investigations, the CRPK with the OXA48-like gene is one of the most common variant among CRE microorganisms (Castanheira et al., 2016). The beginning of carbapenem-resistant Klebsiella pneumoniae (CR-KP) in Turkey and the Middle East presents a considerable challenge to healthcare practitioners due to limited treatment options and high death rates associated with infections caused by these microorganisms (Lee et al., 2016). A previous study found a 50% 30-day mortality rate in individuals with bacteremia caused by OXA-48-producing isolates (Navarro-San Francisco et al., 2013).

Another study found that antibiotic combinations containing a carbapenem have demonstrated poor efficacy in the management of infections caused by CRPK OXA-48-like microorganisms in spite of the low carbapenem MIC values (Stewart et al., 2018). While antibiotic combination cause a high incidence of adverse drug events, an antibiotic combination containing aminoglycosides or colistin has been shown to be effective in several case reports. Ceftazidime/avibactam has been shown to be an important treatment option for CRE isolates due to its activity against Klebsiella pneumoniae Carbapenemase and/or OXA 48-like variants (Stewart et al., 2018).

There are many therapeutic options for CRPK, such as high-dose colistin regimens, high-dose carbapenem regimens (for CRE strains with low MICs), and double carbapenem therapy (Sheu et al., 2019). Ceftazidime-avibactam is an approved therapy option that targets KPC and OXA-48-producing Enterobacteriaceae but it is not recommended to treat metallo-β-lactamase-producing CRE (Sheu et al., 2019).

Ceftazidime-avibactam is a viable therapeutic alternative but its clinical efficacy and outcomes in managing CR-KP infections have not been comprehensively investigated in Saudi Arabia. The aim of the present study is to evaluate the clinical efficacy of ceftazidime-avibactam in managing infections caused by carbapenem-resistant Klebsiella pneumoniae at a single center in Saudi Arabia.

While the CRE Klebsiella pneumonia OXA 48-like gene is endemic and sporadic in Turkey and the Middle East, there have been no clinical studies comparing the CRE in general to the Klebsiella pneumonia OXA 48-like gene in terms of the superiority of ceftazidime - avibactam either alone or in combination therapy (Fawzia et al., 2019). Few studies have examined the efficacy of Ceftazidime-Avibactam in terms of 30-day mortality, clinical remission, and microbiological recurrence rather than microbial eradication (Munoz-Price et al 2013).

There are no studies investigating the effect of different sites of infection as a contributing factor to clinical outcomes other than bacteremia, which was the only studied site of infection in all analyzed research. Key goals include determining clinical remission outcomes, mortality rates, microbiological eradication, recurrence, and factors influencing therapy success or failure. Understanding the efficacy of ceftazidime-avibactam in this setting is critical for improving therapeutic methods and patient outcomes in the face of rising antibiotic resistance.

1.3 Purpose of the Study

We evaluated the superiority of adding the Ceftazidime–Avibactam to the standard therapy by the following endpoints:

1. All deaths within 30 days of culture positive of CRE OXA 48-like gene (mortality rate to be calculated for each arm).
2. Clinical remission or clinical success at the end of therapy by resolving the signs and symptoms of infections such as fever, LAB investigation (CBC, CRP, PCT) and resolving any focus infections X-ray and physical examination (clinical remission rate to be calculated for each arm).
3. bacterial eradication by culture negative at the end of therapy (Microbial eradication rate to be calculated at end of the therapy).

4. bacterial recurrence of the same pattern of the bacteria within 90 days (recurrence rate to be calculated for each arm).

1.4 Research Questions / Hypotheses

1. Is adding the Ceftazidime/Avibactam Antibiotic to standard antibiotic therapy will enhance the clinical outcomes of patients infected with CPKP with OXA 48-like gene in terms of clinical remission, microbial eradication, reducing the rate of microbial recurrence and reducing 30 days all-cause mortality
2. What factors (e.g., patient demographics, infection characteristics, prior antimicrobial exposure) influence the mortality rates of ceftazidime-avibactam treatment infection with CPKP with OXA 48-like gene.

1.5 Significance of the Study

Investigating the clinical efficacy of ceftazidime-avibactam in treating CR-KP OXA-like gene infection in the Middle East is important because it has the potential to enhance patient care, inform treatment guidelines, and contribute to worldwide antimicrobial resistance efforts.

1.6 Limitations

The present investigation was constrained by the retrospective nature of the medium-sized sample with relatively complex co-morbidities. Selection bias could not be completely ruled out, as the research design was not blind in the sense that the investigator did not know which treatment regimen was being employed or which treatment regimen was more successful when paired with CAZ-AVI. The study also lacked more thorough information on infection severity indicators, patients' renal/liver health, and lab work to evaluate pharmacokinetic features in terms of efficiency. Due to the low sample number, we could sub-analyze OXA-48-like variants with or without β-lactamase-resistant mutations. Other empirical antibiotics taken before OXA-48-like antibiotics may have an impact on medication efficacy and mortality that should not be overlooked. Multicenter prospective large studies are suggested to determine the clinical efficiency of CAZ-AVI and which appropriate antibiotic regimen should be added to the concern antibiotic.

CHAPTER II

Literature Review

2.1. Antibiotic resistance

Many bacterial species evolved the ability to tolerate antibiotics long before humans began mass producing them to prevent and treat infectious diseases (Bhullar et al., 2012). Isolated caves (Bhullar et al., 2012), permafrost cores (D'Costa et al., 2011), and other environments and specimens that have been preserved from anthropogenic bacterial contamination can shed light on the resistance mechanisms that existed before the antibiotic era (Lugli et al., 2017; Perry et al., 2016).

The ancient and continuing evolution of resistance mechanisms is likely largely due to the constant competition between microorganisms for resources, including the natural production of secondary metabolites that are similar to many of the antibiotics used as pharmaceuticals today (Davies and Davies 2010; Allen et al., 2010; Martinez, 2009).

The relatively recent use of antibiotics as therapeutic agents has significantly changed the environment that favors the evolution and spread of resistance by imposing unprecedented selection pressures, especially on members of the human and animal microbiota and in environments contaminated with antibiotics. This selection pressure has led to the mobilization and horizontal transmission of a broad spectrum of antibiotic resistance genes in many bacterial species, particularly disease-causing ones (Alcock et al., 2019).

The final, well-known outcome of these cumulative evolutionary processes is a steadily rising level of difficulty in diagnosing, treating, and avoiding bacterial infections. Understanding and identifying the relationships among the human, animal, and environmental microbiota is crucial in addressing this global health issue because genes and bacteria often cross species boundaries and habitat boundaries (Mackenzie and Jeggo 2019; Buschhardt et al., 2021;Wellington et al., 2013; Bengtsson-Palme et al., 2017; Chow et al., 2021; Andersson et al., 2020; Singer et al., 2016; UNEP, 2017; AMR, 2015; Europarl, 2020; WHO, 2020; Graham et al., 2019; Smalla et al., 2018).

Modern medicine and the therapeutic paradigm were completely changed by the discovery, widespread application, and commercialization of antimicrobial medicines for the treatment of infections. Antibiotics are currently thought to be among the most important medical therapies needed for the development of complex medical procedures, such as solid organ transplantation, sophisticated surgical techniques, and the care of cancer patients, according to Munita and Arias (2016).

Unfortunately, the successful treatment of patients in critical condition is currently at risk because of the significant increase in antibiotic resistance among common bacterial diseases. The World Health Organization (WHO, 2014) states that one of the three greatest threats to public health in the twenty-first century is really antibiotic resistance.

Antibiotic production techniques and technologies are evolving these days. The process of creating antibiotics begins with the identification and discovery of antibacterial chemicals. The appropriate microbial strains are then identified and cultivated. Throughout the cultivation process, the choice of co-cultivation or mono-cultivation depends on the microorganism strains' capacity to create antibiotic compounds.

For instance, the antibacterial chemicals needed to synthesize Keyicin are produced by Rhodococcus and Micromonospora bacteria together. Consequently, the co-cultivation method was used to cultivate Rhodococcus and Micromonospora bacteria (Adnani et al., 2017). Industrial antibiotics are typically made using three different processes: fermentation, synthesis, and semi-synthesis. The simplest and least cheap method of making antibiotics is fermentation. However, businesses prefer synthetic and semi-synthetic manufacturing methods since spontaneous fermentation can be unpredictable and difficult to manage. To fight bacteria that are resistant to antibiotics, semi-synthetic antibiotics like tetracycline and dihydrostreptomycin are commonly used as “upgrades” to natural therapies (Leisner, 2020). Telithromycin is one semi-synthetic antibiotic that has proven to be a highly effective treatment for drug-resistant gonorrhoea (Fernandes et al., 2017; Vries and Loeff, 2019).

Synthetic antibiotics are produced via a series of chemical synthesis processes including the modification of naturally occurring active substances' chemical structures by enzymes such as acyltransferases, hydroxylases, and sulfotransferases. For instance, thiamphenicol was made safer for human usage by substituting a methanesulfonyl group for the nitro group in chloramphenicol. This increased thiamphenicol's efficacy and prevented deadly aplastic anemia (Wright et al., 2014). Isolation and purification are the latter stages of the antibiotic-making process, which separate the active components from the impurities. The ion exchange technique is frequently used to separate and purify water-soluble antibiotics, keeping them distinct from other water-soluble drugs and waste organic components. For oil-soluble medicines like penicillin, solvent extraction is the recommended technique (NIA, 2020).

To make the antibiotic powder, the antibiotic is first dissolved in an organic solvent and then recovered using organic chemicals. Antibiotics undergo one more phase of refinement before going on sale, during which they are packaged and transformed into a form that is ready for

use in applications. Preclinical research and clinical trials are the final obstacles to the release of novel medications (NIA, 2020).

To determine the ideal dosage and cytotoxicity of antibiotics, preclinical investigations are carried out both in vivo and in vitro (FDA, 2018). The next step in drug development is clinical trials, which evaluate a medication's safety, effectiveness, and adverse effects in humans (FDA, 2018; NIA, 2020). These days, antibiotic resistance poses the greatest threat to human health. Widespread antibiotic use and antibiotic residues in humans, animals, and the environment may put selective pressure on antibiotic resistance genes (ARG) and bacteria (ARB).

The spread of antibiotic resistance might be accelerated by this. With the growth of ARG, the burden of antibiotic resistance in humans increases, potentially having detrimental effects on people's health (Ding et al., 2023). The use of antimicrobial substances to treat infections has a long history. Several natural extracts were employed for their medicinal properties in antiquity. Several of these extracts, derived from plants and molds, demonstrated antibacterial properties even before the term "antibiotics" was coined (Gould et al., 2016).

The american microbiologist Selman Waksman and associates performed groundbreaking research that resulted in the first use of the term "antibiotics" after they were able to extract substances from microorganisms that may inhibit the growth of other microbes (Clardy et al., 2009). Although the concept of using germs to cure diseases has long existed, modern antibiotic therapy had its start in 1928 when Alexander Fleming made the unintentional discovery of penicillin. By revealing that moldy bread was used by the Egyptians to heal diseases, Fleming's finding contributed to bridging the knowledge gap between the era of antibiotics and ancient knowledge (Muteeb, 2013).

The post-World War II era is recognized as the "golden era" of antibiotic development since it yielded the discovery of numerous antibiotic classes that are still in use today. The idea that infections could be efficiently handled with antibiotics was widely propagated with the introduction of penicillin, despite the earlier use of sulfonamides as the first antimicrobials, which had limitations due to emerging resistance mechanisms that persist to this day (Muteeb, 2013). Interestingly, the penicillin research team also found penicillinase, a bacterium that could break down penicillin, even before the antibiotic was widely available (Muteeb, 2013).

Significant advancements were made in the following decades with the discovery of antibiotics such as cephalosporins, erythromycin, vancomycin, tetracyclines, streptomycin, and chloramphenicol, among others. The age of antibiotics was cemented when formerly incurable diseases could now be treated (Aminov, 2010).

In the years following World War II, semi-synthetic antibiotics gained popularity as well. Examples of these are amoxicillin and quinolones, which are renowned for their enhanced stability and broader bactericidal spectrum. Fighting drug-resistant bacterial species, particularly methicillin-resistant Staphylococcus aureus (MRSA), required the use of vancomycin and other antibiotics. An additional advancement in innovation was made with the creation of daptomycin, linezolid, macrolides, and third-generation cephalosporins, which addressed Gram-negative resistance and enhanced antibiotic pharmacokinetics (Durand et al., 2019; Iskandar et al., 2022; Christensen, 2021).

However, despite these advancements, there has been a rise in antibiotic-resistant bacterial species in recent years. Antibiotic stewardship programs have been established, antibiotic resistance has been more widely recognized, and the usage of antibiotics has been reevaluated. Furthermore, novel strategies such phage treatment, combination medicines, and precision medicine are being researched to tackle drug-resistant bacteria (Chait et al., 2012; Blair et al., 2015; Livermore et al., 2011; Saga and Yamaguchi, 2009).

These alterations are especially noticeable in the gram-negative bacteria (GNB) Enterobacteriaceae family, which is responsible for many infections in hospitals and the general public. Bla is the principal encoder of β-lactamases, which are the main source of resistance in GNB. Currently, over 2100 unique protein sequences are cataloged for this quickly expanding class of β-lactam hydrolyzing enzymes (Bush K.et al,2016). Many of these species include additional plasmid-borne genes that are active against distinct classes of antibiotics, rendering the bacteria resistant to multiple drugs (Jacoby GA et al, 2005).

Few medications exist that can cure GNB infections that are resistant to many drugs (Thomson JM et al, 2005).

Carbapenems, which have long been the final line of defense against the increasingly prevalent carbapenem-resistant Enterobacteriaceae (CRE), are coming under danger from MGEs carrying carbapenemases and other drug resistance genes, infections brought on by multidrug-resistant (MDR) organisms are associated with greater mortality rates than infections produced by susceptible bacteria. Furthermore, estimates of the economic impact of MDR infections in the US alone exceed $20 billion yearly (Sydnor and Perl, 2011).

Conservative estimates from the Centers for Disease Control and Prevention state that at least 23,000 deaths in the US occur annually as a result of infections with antibiotic-resistant organisms (CDC, 2013). Moreover, according to a recent projection, antibiotic resistance might cost the global economy up to $100 trillion (£64 trillion) and cause 300 million avoidable deaths by the year 2050 (AMR, 2014).

The problem is made worse by the absence of a robust antibiotic pipeline, which increases the incidence of infections that are almost completely incurable and leaves doctors without reliable options for treating patients.

2.2. Carbapenem-Resistant Klebsiella pneumonia

Gram-negative Klebsiella pneumoniae is an opportunistic pathogen that is found in the human microbiome. It can cause a variety of ailments, including bloodstream, urinary tract, and hospital-acquired infections (Hansen et al., 1998). The use of cephalosporins, aminoglycosides, fluoroquinolones, and, as a last resort, carbapenem medications is the clinical treatment for these infections. However, manufacturing cephalosporinases or extended-spectrum beta-lactamases in combination with porin alterations, or obtaining resistance genes that encode carbapenemases, are the main methods that Klebsiella pneumoniae may develop resistance to carbapenems (Bush, 2018).

Carbapenemase genes are particularly harmful because they have the ability to multiply in conjunction with mobile genetic elements (MGE) present in plasmids and transposons. Most commonly, these carbapenemase genes (blaKPC, blaNDM, blaVIM, and blaOXA-48) are associated with particular and efficacious nosocomial clones. In some instances, they also have a close relationship with the determinants of antibiotic resistance within a lineage (Munoz-Price et al., 2013).

The most common K. pneumoniae carbapenemases (KPC) are imipenemase (IMP), oxacillinase (OXA-48-like), and New Delhi metallo-β-lactamase (NDM) (Hamza et al., 2024). A few drugs, such as colistin, tigecycline, aminoglycosides, and in some cases, ceftazidime/avibactam, can be used to treat CPKP. Due to the blood-brain barrier's low penetration, the majority of medications have difficulty reaching the minimum inhibitory concentration (MIC) in the cerebrospinal fluid (CSF) (Hamza et al., 2024).

Extended spectrum β-lactamase (ESBL)-producing Gram-negative Enterobacteriaceae infections have become increasingly common in nosocomial settings and are associated with considerable morbidity and mortality. The issue has gotten worse due to the advent of strains that can produce carbapenemase, which reduces the effectiveness of carbapenem therapy. According to Veeraraghavan et al. (2017), bacteremic diseases are frequently associated with Acinetobacter baumannii-calcoaceticus complex (Abcc) and Klebsiella pneumoniae, the two most common multidrug resistant bacteria.

Due to the widespread usage of carbapenems, there have been more reports worldwide of the emergence of CRKP (Carbapenem-resistant Klebsiella pneumoniae) (Zhao et al., 2019; Gu et al., 2018). CRKP was considered a serious threat to global health, per several reports (Karampatakis et al., 2018). Carbapenem-resistant Klebsiella pneumoniae (CRKp) is a prevalent pathogen that causes nosocomial infections with a high fatality rate and dismal prognosis (Wang et al., 2024).

Klebsiella pneumoniae is a non-motile Gram-negative opportunistic pathogen that accounts for around 10% of nosocomial bacterial infections. Infections caused by isolates of carbapenem-resistant K. pneumoniae (CRKP) pose a major concern to public health. These infections can increase the mortality rates of patients in intensive care units (ICUs) and have a negative impact on hospitalization costs for critically ill and disabled patients globally (Katsiariet al., 2015; Zhen et al., 2020; Ahmadi et al., 2022; Sarshar et al., 2020).

The effect of CRKP infections on disability-adjusted life years (DALYs) per 100,000 population is a significant public health problem. Greece has one of the highest median DALY rates (11.5) among the European Union's member states (Cassini et al., 2019). According to the ECDC (2019), the proportion of K. pneumoniae isolates resistant to carbapenem in Greece was 66.3% in 2020. A recent meta-analysis shows that, whereas the prevalence of CRKP colonization varies globally from 0.13 to 22% with a pooled prevalence of 5.43%, the incidence of CRKP colonization varies from 2% to 73% with a pooled incidence of 22.3% (Tesfa et al., 2022).

Worldwide, death rates from carbapenem-susceptible K. pneumoniae (CSKP) infections vary from 33 to 50% (Xu et al., 2017), a much higher rate than that from infections with carbapenem-resistant K. pneumoniae (CRKP) (WHO, 2014). Thus, avoiding CRKP infection is essential to avoiding a poor prognosis and potentially even mortality, as well as preventing widespread transmission of carbapenem resistance through mobile genetic elements (Yigit et al., 2001).

2.2.1. Molecular mechanism and classification of carbapenem resistance in Enterobacteral

Phenotypic resistance to carbapenems is typically caused by two main processes: the combination of β-lactamase activity with structural changes (Bush K, et al 2011) and the formation of carbapenemases, which are enzymes that hydrolyze carbapenem antibiotics (Siegel JD, et al 2007). The first mechanism involves the production of extended-spectrum β-lactamases (ESBLs), which are usually encoded by plasmids, and AmpC cephalosporinases (AmpC), whose expression in Enterobacteriaceae is typically linked to the hyperproduction of enzymes from inducible or depressed chromosomal genes (Bush K, et al 2011).

ESBLs and AmpC can confer carbapenem resistance when combined with the mutation of porins, a family of GNB outer membrane proteins that, when altered or absent, can slow the diffusion of antibiotics across the bacterial membrane to a pace slow enough to facilitate the action of the enzymes (Paterson DL, et al 2005, Jacoby GA, et al 2009). Two more mechanisms associated with carbapenem-resistance in GNB include modifications to penicillin-binding proteins and drug efflux pumps, based on their molecular structures, carbapenemases fall into one of three classes of β-lactamases (Class A, B, and D) under the Ambler classification system (Bush K, et al 2011).

Class A and D carbapenemases require serine in their active site, whereas class B, the metallo-β-lactamases (MBLs), require zinc for β-lactam hydrolysis (Bush K, et al 2011). Notable examples of class A carbapenemase genes are Klebsiella pneumoniae carbapenemases (KPCs), Serratia marcescens enzyme (SME), Serratia fonticolacarbapenemase (SFC), Guiana extended spectrum (GES), imipenem resistance (IMI), and non-metallocarbapenemase-A (NMC-A). KPCs are the class A genes that are most commonly transmitted worldwide in Enterobacteriaceae infections (Patel G, et al 2013). KPCs have the ability to hydrolyze all β-lactams, and isolates with blaKPC often become resistant to trimethoprim-sulfamethoxazole, aminoglycosides, and fluoroquinolones, which can result in MDROs (Nordmann P, et al 2009). Due primarily to the clonal expansion of K. pneumoniae strains associated with clonal complex 258 (CC258) and, more specifically, multilocus sequence type (ST) 258 strains carrying a blaKPC-2 or blaKPC-3 gene situated on a Tn3-based transposon, Tn4401, KPC-producing Enterobacteriaceae have spread throughout the world (Cuzon G, et al 2011). However, the dissemination of blaKPC is far more complex. A multitude of different sequence types that carry blaKPC, which is connected to several plasmids, are united to the two distinct genetic clades (I and II) that comprise the circulating ST258 K. pneumoniae strains (Carattoli A, et al 2009, Chen L, et al 2014).

Furthermore, the lowest inhibitory doses of KPC-producing bacteria range from sensitive to >16 μg/mL, indicating various degrees of resistance to carbapenem. These changes are associated with losses of outer membrane porins (OmpK35 and/or OmpK36), deletions that occur directly upstream of the blaKPC gene, and/or an increase in the number of copies of the blaKPC gene (, Patel G, et al 2013, Kitchel B, et al 2010). The class D OXA β-lactamases are a diverse group of enzymes that are named jokingly because of their capacity to hydrolyze oxacillin. Enterobacteriaceae, especially the OXA-48 types, are where they are being found more and more (Poirel L, et al 2010).

The most common basis associated with the spread of Enterobacteriaceae that produce OXA-48 is an IncL/M-type plasmid that has integrated the blaOXA-48 gene by acquiring a Tn1999 composite transposon (Poirel L, et al 2010, Carrer A, et al 2010). OXA-48 enzymes hydrolyze penicillins at a high level and carbapenems at a low level, sparing extended spectrum cephalosporins; nevertheless, some bacteria express several ESBLs, rendering them resistant to all β-lactams (Poirel L, et al 2012).

Commercially available β-lactamase inhibitors do not inhibit the complicated group of enzymes known as class B MBLs, which hydrolyzes all β-lactams except for monobactams (Bush K, et al 2011, Patel G, et al 2013). Unlike serine carbapenemases, they require zinc for β-lactam hydrolysis, hence metal-chelating substances such as ethylenediaminetetraacetic acid (EDTA) inhibit their activity (Bush K, et al 2011, Patel G, et al 2013).

Three well-known transmissible MBL genes in Enterobacteriaceae are VIM (Verona integron-encoded MBL), NDM (New Delhi MBL), and IMP (active on imipenem) (Bush K, et al 2011, Walsh TR, et al 2010). The homology of amino acid sequences between the three MBL subclasses (B1–B3) allows for differentiation; almost all acquired MBLs with clinical significance belong to subclass B1 (Mojica MF, et al 2016). Transposons and plasmids, which are most commonly embedded in class I integrons, are connected to MBLs of the VIM and IMP kinds, helping to spread them (Patel G, et al 2013).

Although Enterobacteriaceae that produce KPC and NDM spread swiftly, the spread of NDM-type MBLs is facilitated by numerous types of plasmid incompatibility (Inc) and appears to be unrelated to dominant clonal strains (Walsh TR, et al 2010). The most common circulating NDM MBL gene in Enterobacteriaceae (blaNDM-1) is thought to have originated from Acinetobacter baumannii. According to Dortet L. et al. (2012) and Dortet L. et al. (2014), this opinion is supported by the full or variant insertion sequence ISAba125 upstream of the blaNDM-1 gene in both blaNDM-carrying A. baumannii and Enterobacteriaceae, as well as the similar coexpression of blaNDM with bleMBL, a gene that confers resistance to the cancer drug bleomycin, in both genera of blaNDM.

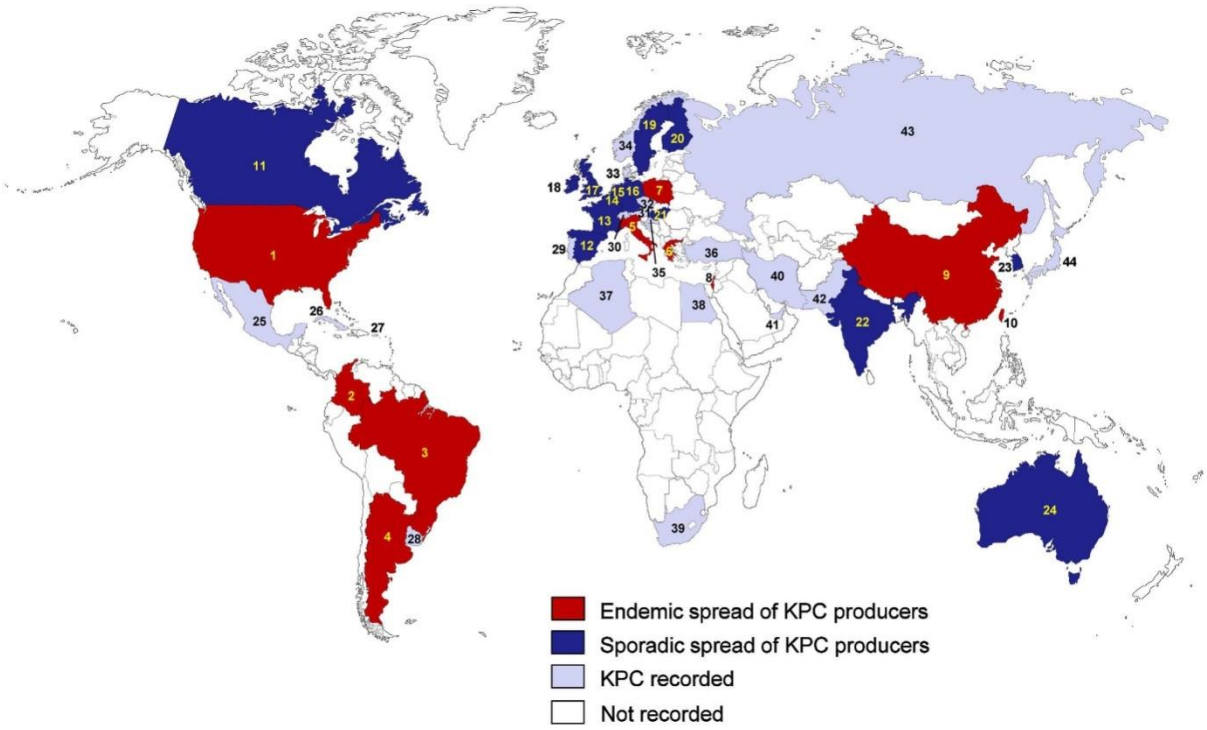
Several epidemic clones, including K. pneumoniae ST11 and ST147 and Escherichia coli ST131 and ST101, have been found to carry NDM-type MBL genes, as well as β-lactamase genes and antibiotic resistance determinants (Patel G, et al 2013, Walsh TR, et al 2010, Dortet L, et al 2014). The rapid spread of NDM MBLs is thought to be due to the promiscuity of the genetic components (Dortet L, et al 2014). Epidemiologically and therapeutically, it is critical to distinguish between carbapenemase-producing (CP) and non-CP CRE; nonetheless, susceptibility patterns and treatment suggestions are what healthcare professionals seek. The

Centers for Disease Control and Prevention (CDC) have updated their guidelines, which can help guide definitions and testing considerations in CRE diagnosis and therapy (CDC, 2016).

2.2.2. Class A Carbapenemases

Six distinct class A carbapenemases have been identified as forming distantly related branches, some were encoded on chromosomes, while others were encoded on plasmids. KPC enzymes, are the most commonly observed class A carbapenemases since they were initially described in the United States in 1996 (Yigit et al., 2001).

Figure 1



spread of KPC producers Klebsiella pneumonia adopted from Munoz-Price et al., 2013

KPC family comprises several variants, the best defined of which are KPC-2 and KPC-3 (KPC-1 to KPC-22). The bacteria that manufacture KPCs are resistant to aminoglycoside antibiotics, tigecycline, and colistin. Most KPCs are plasmid-encoded. As a result, individuals who get bloodstream infections due to these bacteria have a very high fatality rate (De Rosa M, et al 2021).

Epidemiological reports describing the distribution of KPC variants mainly in North American, Latin and China according to Munita JM et al. (2016). A number of countries in Far East, Australia, and India, as well as several western states, the United Kingdom, have also reported occasional distribution of KPC variants (Darby EM 2023).

Predominant route of CR K. pneumoniae transmission in the United States is the multiplication of organisms harboring KPC enzymes, despite the evolution of defferent carbapenemase

enzymes such as NDM (Kaiser et al., 2013). The frequency of KPC variants in the USA from 2007 to 2009 was 5.9% in 2007, 4.9% in 2008, and 5.7% in 2009, according to Kaiser et al. (2013).

There have been reports of KPC variants in the USA (Munita JM 2016). More recently, though, endemic care facilities have also been linked to outbreaks that have been reported in several European nations. Given that KPC variants have been discovered to exist in France, and Greece (T sakris et al., 2008).

Additionally, the KPC variants have been detected in a number of eastern European countries, including the UK, Ireland, Belgium, Sweden, Croatia, Hungary, and Finland (Kanerva et al., 2015; Samuelsen 2009; RobustilloRodela 2012).

The frequency of KPC variant increased from 0% in 2003 to 38.3% in 2010 among isolates obtained at a tertiary Greek hospital. Most of them had KPC-2 (Zagorianou 2012).

Moreover, K. pneumoniae that produces KPC has been detected in Mexico (Garza-Ramos et al., 2014), Cuba (Quinones et al., 2014), Puerto Rico (Gregory et al., 2010), and Uruguay (Marquez et al., 2014). Moreover, KPC-producing ST11 strains have been reported from Latin America (Munoz-Price et al., 2013). While India (Shanmugam et al., 2013), South Korea (Yoo et al., 2013), have observed occasional spread, China and Taiwan (Tseng et al., 2015) have shown endemic KPC-producing K. pneumoniae dispersion. Nearly identical to KPC-4, a new KPC-15 variation was observed in China (Wang et al., 2014a).

2.2.3. Class B Carbapenemases

Class B carbapenemase, also called metallo-b-lactamases, which need zinc to catalyze the reaction. They can hydrolyze nearly any b-lactam antibiotic, including carbapenems, and have a broad substrate range, (Jiang Y 2015). Examples of that class predominantly detected include VIMs, IMPs, and the recently identified NDM group (Jiang Y, 2015). NDM is one of the most clinically significant carbapenemases.

NMD 1initially discovered with patient travelled to Sweden coming back from india then that strain NMD1 was distributed to the world later in 2008 (Jiang Y,2015).

Previous study (Jeon et al., 2015) reported the identification of 15 NDM variants, the bulk of which were found in Asia. Nordmann and Poirel (2014) state that there aren't many similarities between NDMs and other metallo-b-lactamases. Since 2008, NDMs that produce K. pneumoniae have spread swiftly to many different states, The NDM is believed to be distributed endemically Bangladesh, India, and Pakistan (Giske CG, 2012).

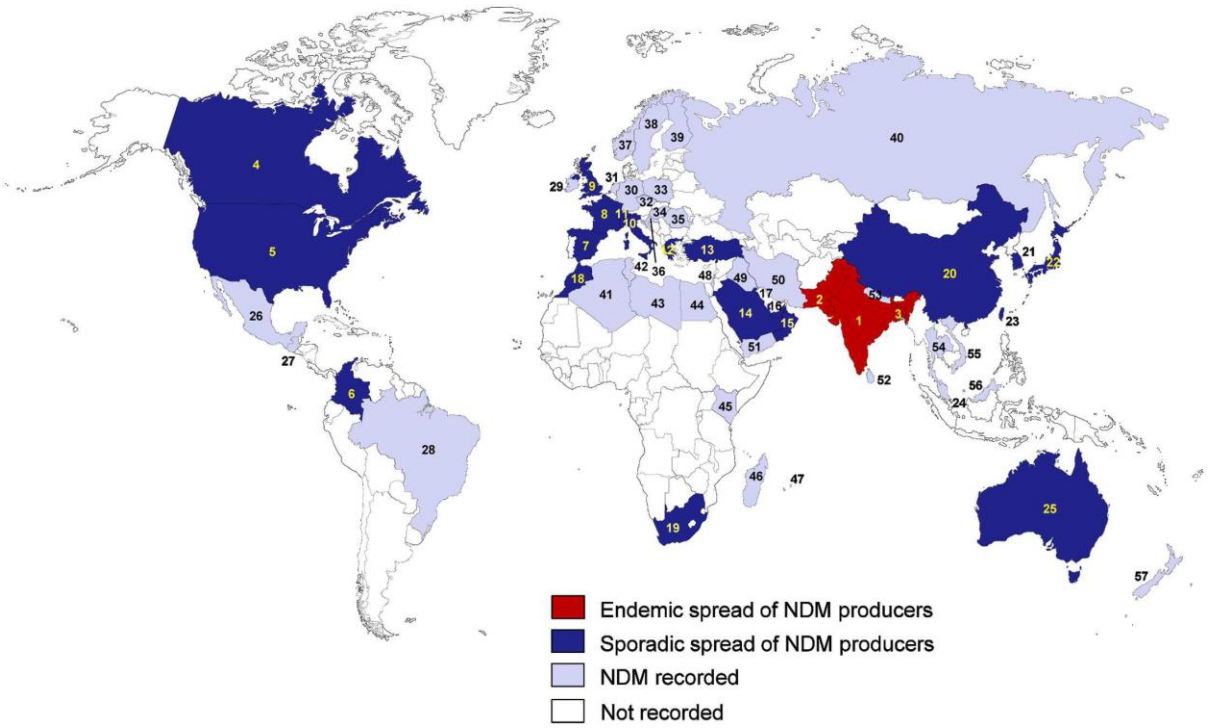


Figure 2

spread of NDM producers Klebsiella pneumonia adopted from (Berrazeg et al., 2014)

Numerous nations, including the United States, Colombia, Spain, France, Switzerland, Italy; the United Kingdom, Greece, Turkey, Morocco, South Africa, Singapore, Arabian Peninsula, China, Japan, Taiwan, South Korea, and Australia have all recorded cases of sporadic spread (Cornaglia G, 2004)

The most common kind of carbapenemase, NDM-1, was produced by more than 75% of the isolates that produced it in India, other states that discovered with high prevalence of NDM1 are Singapore, United Kingdom and Emirates, as there are receiving many expactriates from Pakistan and India.

Other regions that have been suggested as potential new sources of NDM production include the North African nations (Dortet et al., 2014c). Out of 132 non-repetitive CRE isolates, Voulgari et al. reported that 78 variants carrying the bla NDM 1 gene were discovered in Greece between 2010 and 2013 (Voulgari, 2014).

Many countries, including Mexico, Guatemala, Brazil, the Netherlands, Ireland, Poland, the Czech Republic, Croatia, Russia, Tunisia, Romania, Egypt, Kenya, Madagascar, Iraq, Yemen, Iran, Mauritius, Sri Lanka, Thailand, Nepal, Vietnam, Malaysia, and New Zealand have detected NDM-producing K. pneumoniae as a result of patient mobility across international borders (van Duin D,2017).

NDM variants is spreading around the world, and this has a major impact on newborn death rates. Particularly in developing countries, where infant sepsis is frequently seen, (Zaidi et al., 2005).

According to Datta et al. (2014), sepsis was caused more frequently by isolates carrying NDM-1, and 14% of the Enterobacteriaceae isolates, including K. pneumoniae, which is the blood isolates of newborns experiencing septicemic episodes in India carried bla NDM 1. A neonatal facility in China had an outbreak of the NDM variants ST20 and ST17 isolates.

(Poirel et al. 2014) reported on the spread of K. pneumoniae that produces NDM-1 in a neonatal intensive care unit in Turkey.

Coexistence of NDMs with defferent variants have been documented in Turkey (NDM-1/OXA-48; Kilic and Baysallar, 2015), Pakistan (NDM-1/KPC-2; Sattar et al., 2014), Switzerland (NDM-1/OXA-48; Seiffert et al., 2014), the United Arab Emirates (NDM-1/OXA-48-like; Dash et al., 2014).

2.2.4. Class D Carbapenemases

Since they frequently hydrolyse isoxazolylpenicillins like oxacillins more frequently than other pencillins as that varians hold a gene of Oxacillinase, that varians divided to 12 types of Oxacillinases based on their nuclic acid consequences of them four variants can expressed by Klebsiella pneumonia (Docquier J-D,2009).

OXA 48 variant initially discovered in Turkey in 2001 and consider as a reservoir for all other countries mainly in Meddile East, North African and Arabian Peninsula (Poirel L,2004).

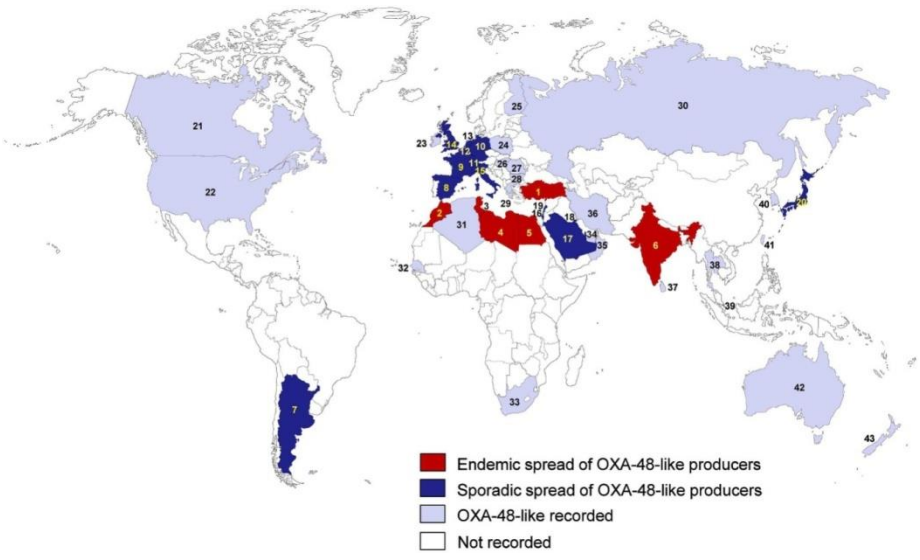


Figure 3

Spread of OXA-48 like producers Klebsiella pneumonia adopted from Espedido et al., 2013

That variant distributed sporadically which documented in various countries, including Spain, Italy, Belgium, the Netherlands, the United Kingdom, Germany, Switzerland, Argentina, Lebanon, Kuwait, Saudi Arabia, and Japan (Semin-Pelletier et al., 2015).

In Saudi Arabia, there is three strains of the 47 blaOXA-positive isolates were resistant to colistin, and 78% of the isolates in the nation had blaOXA-48 (Shibl, 2013).

Although OXA 48 variant mainly distributed in Middle East and North Africa , there is few reports about the outbreak in some European hospitals suggesting that distribution due to the lack of infection controls measures and strick guidelines such as University hospital , Germany and French University hospital in Paris, (Kola , 2015)

Sporadic spread has been documented in several countries, including Spain, Italy, Belgium, the Netherlands, the United Kingdom, Germany, Switzerland, Argentina, Lebanon, Kuwait, Saudi Arabia, and Japan (Semin-Pelletier et al., 2015). Only 11% of that isolates from North America included OXA-48-like enzymes (Lascols et al., 2013).

A Romanian study indicated that blaOXA−48 (78%), bla NDM−1 (12%), and bla KPC−2 (6%) were the most frequently discovered genes among 65 K. pneumoniae strains producing carbapenemase. OXA-48 and OXA-244 have been found in Proteus mirabilis, E. aerogenes, E. cloacae, and K. pneumoniae, and they have lately spread throughout Russia (Fursova et al., 2015).

There are few reports about the distribution of OXA48 harbouring with NDM 1 in some countries such as Turkey and western europes and Arabian Peninsula (Shaidullina E, 2020).

2.3. Treatment of Carbapenem-Resistant Klebsiella pneumonia producing

The World Health Organization (WHO, 2017) categorized carbapenem-resistant Enterobacterales (CRE) as the "critical" group of bacterial infections posing the greatest risk to human health. Given the gravity of the threat posed by CRE and the high global mortality rate, epidemiological monitoring is critical (Verdugo-Paiva et al., 2022). The rising rate of resistance among non-fermenting bacteria and members of the Enterobacteriaceae family jeopardizes the availability of effective antibiotics, which are a cornerstone of contemporary treatment (Fritzenwanker et al., 2018). There are limited therapeutic options for severe nosocomial infections caused by carbapenem-resistant Klebsiella pneumoniae.

A growing corpus of data shows that combination antibiotic therapy outperforms monotherapy in terms of efficacy. However, there are still issues about the optimum regimen and how to balance the benefits of combination therapy against its risks and potential downsides (such as toxicity, increased costs, and Clostridium difficile infection) (Watkins &Deresinski, 2015).

Antimicrobial resistance is widely recognized as one of the most serious threats to community health. Multidrug resistant Gram-negative rode infection are particularly worrying because they are becoming increasingly frequent over the world. The increasing level of Gram-negative antibiotic resistance is mostly caused by enzymes known as ß-lactamases, which bind to and deactivate ß-lactam antibiotics, rendering them worthless. For many years, carbapenems have been used successfully to treat patients infected by resistant enterobacteral such as Klebsiella pneumoniae and E coli. These bacteria can create extended spectrum ß-lactamases (ESBLs), a type of ß-lactamase that is resistant to monobactams, cephalosporins, and penicillins (Morrill et al. 2015).

Carbapenem-resistant Enterobacteriaceae [CRE] are a type of bacteria that confer broad resistance to the majority of ß-lactam antibiotics, including "last-line" carbapenems (Morrill et al., 2015). These bacteria make carbapenemases. To achieve a synergistic effect, a number of in vitro active substances, including colistin, tigecycline, and, more recently, ceftazidime/avibactam (CAZ-AVI) or Meropenem/Vaborbactam (MER-VAB), have been used alone or in combination with not susceptabple in vitro medications, such as meropenem. All three drugs were administered at high doses (colistin 9 MU/day, tigecycline 200 mg/day, and meropenem 6-11 gr/day). Prior to the approval of novel β-lactam/β-lactamase-inhibitor combinations (e.g., CAZ-AVI and MER-VAB), observational studies found that combination therapy improved clinical success and mortality rates (Daikos et al., 2014; Tsuji, 2019; Spaziante, 2020).

There are few treatment options for CRKP, but older drugs such as aminoglycosides, polymyxins, glycylcycline, and fosfomycin can be effective in vitro. However, therapies for polymyxins such as colistin and polymyxin B (PMB) have negative effect on kidney and neurotoxicity (Qu, 2022). Ceftazidime-avibactam (CAZ/AVI) is a combination of the cephalosporin ceftazidime and the novel β-lactamase inhibitor (BLI), avibactam. CAZ/AVI is highly effective against Gram-negative bacteria in vitro, including Ambler class A- (Klebsiella pneumoniae carbapenemase), class C-, and certain class D β-lactamase enzymes. However, it has little activity against bacteria that manufacture Metallo-β-lactamase (MBL) (Chen et al., 2021).

CAZ/AVI has been licensed by the European Medicines Agency, the Chinese Food and Drug Administration, and the American FDA to treat of severe urinary infections, hospital-acquired pneumonia, and difficult intra-abdominal infections (Matesanz et al., 2021). To our knowledge, few multicenter trials have investigated the efficacy of PMB and CAZ/AVI for CRKP infection. Furthermore, there is a scarcity of data comparing PMB and CAZ/AVI, or their combinations, in terms of CRKP infection in Saudi populations.

2.3.1. Treatment of Class A Carbapenemase-Producing Klebsiella pneumoniae

According to Ducomble (2015) they consider that KPC variants as the major hospital acquired infection which reflect negatively outcomes to the ctitically ill patients' outcomes especially in case of nosocomial blood stream outbreaks.

Despite KPC variants has multidrugs resistant mainly against penicillins, second, third generation cephalosporin and flouroqiunolones, some antibiotics medications still reserve their activity against that variants, Aminiglycoside, Fosfomycin, Colistin and Tigecycline cosider as a good choice in treatment of KPC variants (Federico P,2017)

Acoording to Adams- Haduch et al., 2009 temocillin has efficacy against some KPC variants, particularly in cases of lower urinary tract infections.

Combined therapy is occasionally recommended to improve germ killing and prevent bacterial resistance. Treatment of colistin-resistant KPC, was considerably improved by carbapenem-based combination therapy, such as tigecycline, colistin, and meropenem (Tumbarello et al., 2012).

Conflecting Data about the combination therapy of Rifampicin add on to Colistin to treat patient infected with KPC variants comparing to Colistin Monotherapy, extensive researchs required to evaluate which comination regmin will be more effective in case of that KPC variants especially with high activity of Omp K35, Omp K36 expression as they are the only ones are responded to triple Antibiotc regemin of Colistin Add on to double Carbapenems (Bulik CC et al,2011)

Colistin (polymyxin E), developed over 55 years ago, is a crucial antibiotic of a regimens used to treat severe KPC variants infections, Since KPC variant became widespread worldwide, reports of colistin resistance in KPC have emerged in a number of countries, including Greece Italy, the United States Hungary and Turkey. That Colistin resistant KPC blood stream isolate put the global health in threat due to high mortality and morbidity (Bogdanovichetal., 2011).

An antibiotic with a wide range of effects, Fosfomycin, inhibits the biogenesis of bacterial cell walls by deactivating the enzyme found in the peptidoglycan cell wall so it is effective for both gram positive and gram-negative organism especially if combined with betalactam and aminoglycoside antibiottics (Falagas ME et al 2008)

That unique antibiotics has special pharmacokinetics parameters with long half life and massive penetration to the GI and urinary tract infection, more than 80% of Colistin and Tigecycline resistant KPC variant still sensitive for Fosfomycin (Pontikis K et al 2014)

Despite a few reports about the low incidence of Fosfomycin resistant KPC variants a study in china with more than 12 hospitals reveal a more than 40% resistant organisms , approximately reports from Japan with the same results (Wachino et al 2015).

Tigecycline is a Tetracyline derivative antibiotics approved to be used in patient with KPC variant with complicated intra abdominal infection , complicated soft tissue infection , also it is effective in case of community acquired pneumonia , blood stream infection as in combination regemin with Colistin , Carbapenems and Aminoglycoside , some reports recommend using high dose strategy of 100 mg twice daily in case of VAP with KPC infections (Brust K et al 2014).

According to (Tzouvelekis et al., 2014) , a combination antibiotic regemin of Aminoglycoside with traditional dose of Tigecycline is effective to treat sepsis patients with KPC infections .

Additionally, the efficacy of a few drugs against K. pneumoniae, the bacteria that causes KPC, was evaluated. Strong inhibitors of novel betalactamase inhibitor, including avibactam and MK7655, have been shown to be effective in treating KPC variants . According to Wang et al., 2014e, avibactam and ceftazidime combination therapy shown notable synergistic effects against organisms carrying combinations of KPC-2, AmpCs, and extended-spectrum b-lactamases (ESBLs).

Plazomicin, a recently synthesized aminoglycoside, has demonstrated notable efficacy against K. pneumoniae, which generates KPC, according to Temkin et al. (2014). It is being developed to create novel polymyxin compounds with reduced nephrotoxicity (Vaara, 2010). A recent study (Ribeiro et al., 2015) found a peptide has an antibacterial quality provide a potential treatment for infections caused by K. pneumoniae, which generates keratin (KPC).

An Aminoglycoside new antibiotic called Plazomicin was tested both alone and in combination with standard antibiotic regemin against strains of KPC that produce carbapenemase. Combining plazomicin with meropenem, colistin, or fosfomycin showed a synergistic impact towerd KPC infections (Livermore DM et al 2011).

2.3.2. Treatment of Class B Carbapenemase-Producing Klebsiella pneumoniae

Class B variants contain few variants mainly New Delhi metalo B lactamase bactria which mostly resistant to novel antibioitcs such as CAZ-AVI which is effective to other variants and a report with regards to antibiotic activity recommend to use Aztreonam as a combination therapy with either CAZ-AVI or a standard therapy (Mauri te al 2021).

Additionally, it has been shown that a combination of colistin and fosfomycin therapy works synergistically in vitro against the NDM-producing K. pneumoniae (Lodise et al., 2020).

Colistin and chloramphenicol together dramatically improved bactericidal effect and inhibited developing resistance to Colistin when used against K. pneumoniae, which generates NDM (Paul et al 2021).

Acoording to Wunderink (et al 2021) new medication antibiotic called Cefodericol which effective for many varians of CRE and specifically the NDM 1 as a monotherapy or in combination with standard therapy as compared with standard therapy alone with high dose of Carpabenems in reducing the mortality more than 12% and improving the clinical cure more than 70% and microbial eradication more than 60%.

2.3.3. Treatment of Class D Carbapenemase-Producing Klebsiella pneumoniae

According to Laishram et al. (2015), this implies that figuring out the kind of carbapenemase aids in figuring out the combination that has the best chance of curing the infection. According to Evren et al. (2013), imipenem, meropenem, and tigecycline when combined with fosfomycin showed synergistic effects against K. pneumoniae strains that were positive for OXA 48.

CAZ-AVI still posses promising effect in case of that variants as a monotherapy and in combination therapy in term of clinical cure eradication and all cause mortality (AbuJaber et al 2024).

New promising novel beta lactamase inhibitor is zidebactam add to Firth generation cephalosporin Cefepime has excellent activity against class D variants (VanScoy BD et al 2016).

One report from Paredo (et al 2013) screening one Spanish hospital observed that OXA48 like gene Klebsiella pneumonia has multi drug sensitive to Aminoglycoside more than 90% , Colistin more than 90% , Tigecycline more than 70% and Fosfomycin more than 60% with a mortality rate more than 40% .

2.4. Carbapenems resistance Klebsiella pneumonia in Saudi Arabia

2.4.1. Prevalence and regional distribution of CRE reports from Saudi Arabia

The Enterobacteriaceae species found in Saudi Arabia are increasingly being reported to be resistant to carbapenem. The proliferation of carbapenem-resistant genes and the rise in the frequency of CRE producers are of particular concern to medical professionals and the Saudi Ministry of Health. The capital of Saudi Arabia, Riyadh, is where most reports pertaining to CRE come. On the other hand, little information is available regarding the genetic characteristics of Enterobacteriaceae or the pattern of their susceptibility to carbapenem in studies conducted in various regions of Saudi Arabia.

Ipenem was effective against every isolate, according to a recent Madinah study that evaluated the antibiotic susceptibility of Klebsiella pneumonia from multiple clinical sources (Saeed et al., 2018). In a recent study, Al-Zahrani and Al Asiri analyzed the molecular characteristics of 54 K. pneumoniae isolates obtained from clinical specimens from two of the largest hospitals in the Southern province of Saudi Arabia that were not responsive to carbapenem. The most common type of carbapenemases found was OXA-48 (81.5%), followed by NDM (7.3%). Al-Zahrani IA et al. (2018) reported that only a single isolate of Verona integrin encoded metallo-β-lactamase (VIM) was found. The Makah non-molecular phenotypic research (Khan et al., 2016; Faidah et al., 2017) determined that K. pneumoniae producing carbapenemase accounted for 48.4% and 38% of the total.

The first study in Saudi Arabia and the Gulf region to evaluate CRE and carbapenem-resistant Pseudomonas aeruginosa (CRPAE) colonization of the digestive tract was carried out in Dammam. This study found that gastrointestinal tract colonization with CRE occurred in just 0.5% (1/200) of patients admitted to intensive care units (Abdalhamid et al., 2016). Another fascinating study from Jeddah city discovered that during the Hajj event in October 2013, there was a significant incidence of blaNDM-1-positive Klebsiella pneumonia in the local wastewater. Bla NDM-1 concentrations in raw wastewater ranged from 104 to 105 copies per m3 (Mantilla-Calderon et al., 2019).

Numerous investigations have been conducted in Riyadh, which is located in the central region of Saudi Arabia (Balkhy et al., 2012, Zaman et al., 2014; Al-Agamy et al., 2018; Marie et al., 2013; Memish et al., 2015; Zaman et al., 2018; El Ghany et al., 2018; Yezli et al., 2017; Alotaibi Fawzia et al., 2017; Shibl et al., 2013; Al-Agamy et al., 2013). These included reports describing small outbreaks, molecular characterization of CRE, and a matched case-control study (Garbati et al., 2016) that detailed the number of cases, the regional distribution, the molecular characteristics of CRE isolates, and the main conclusions of nearly all reported CRE

studies from Saudi Arabia. Studies highlighting the emergence and persistence of specific carbapenem resistance genetic deterrents in hospitals (Zaman et al, 2014).

2.4.2. Prior hospitalization and travel history

NDM and OXA-48 carbapenemases may have established themselves in Saudi Arabia as a result of foreign travelers bringing resistant Enterobacteriaceae strains with resistance traits into the country. The origins and increasing dispersion of CRE could be attributed to the extensive migration that takes place, particularly during the Hajj seasons, between the Kingdom and other countries like India, where NDM is endemic. 23.3% of the CRE-infected patients in the Gulf region reported having traveled abroad (Alotaibi, 2019).

According to Sonnevend A. et al. (2015), Pakistan, Africa, and India are the most popular travel destinations. Moreover, some research has revealed that visiting Middle Eastern countries such as Saudi Arabia can result in the acquisition of OXA-48 carbapenemases (Sonnevend et al., 2015). In fact, the first-ever case of carbapenem-resistant, OXA-48-producing Klebsiella pneumoniae in US history was found in a patient who had recently been admitted to a Saudi Arabian hospital (Mathers et al., 2013). Compared to bla OXA-48-like and bla VIM, the bla NDM primarily found in isolates obtained from patients who had traveled in the past (Sonnevend et al., 2015).

Prior hospitalization is a significant risk factor for the acquisition of CREs; in one study, this was observed in 72.3% of the patients (Garbati et al., 2016). A multi-resistant pattern to antibiotics other than carbapenem was also observed in isolates from individuals who had previously been hospitalized, traveled, or both (Garbati et al., 2016). However, of the 96 CRE cases collected from the Gulf region, 69.8% had no record of travel or hospitalization abroad (Sonnevend et al., 2015). It follows that the principal source of CRE transmission to Europe and other distant locations is believed to be the Middle East and other Asian countries. Early identification and screening of patients who had previously been hospitalized in the Middle East for CRE, particularly the highly transmissible strains such those that produce NDM-1, was found to be an effective infection control technique (Birgy et al., 2011).

2.4.3. Types of CRE species

Within the Enterobacteriaceae genus, carbapenemases are more prevalent in K. pneumoniae isolates, which usually leads to outbreaks and hospital-acquired infections. Balkhy et al. (2012) reported the first nosocomial outbreak, which comprised 23 cases of carbapenem-resistant K. pneumonia. In a study by Makah, some of the most frequently isolated species were Escherichia coli, Klebsiella pneumoniae, and Enterobacter sp. (Faidah et al., 2017). Apart from a comprehensive study that described the molecular identification of the β-lactamases in K. pneumoniae and E. coli from a tertiary care hospital in Riyadh, it was observed that K. pneumoniae had more carbapenemase genes (63%) than E. coli (55%).

2.4.4. Risk factors associated with the acquisition, emergence and spread of CRE

There are several risk factors associated with the emergence and spread of CRE in Saudi Arabia. Anticipatorily, the extensive use of carbapenems as first line therapy for invasive infections caused by Enterobacteriaceae producing ESBL is a major risk factor for the development of CRE. The creation and spread of CRE strains in Saudi Arabia and the Gulf region are believed to be largely caused by a number of reasons, including the widespread immigration of different populations, especially from Asia (India), and the unrestricted use of antibiotics (Sonnevend et al., 2015).

There are two well-known risk factors for the spread of multi-resistant organisms like CRE: traveling overseas during religious ceremonies and moving patients with resistant strains from one nation to another (Sonnevend et al., 2015). Further possible risk variables were reported from Saudi Arabia in a matched case-control study of 29 cases and 58 controls of hospitalized Saudi patients. According to the study, invasive surgeries, length of hospital stay, comorbidities, and usage of carbapenem in the past were all strongly linked to CRE infections. Additionally, an independent association between renal disease requiring dialysis and CRE infection was discovered (Garbati et al., 2016).

2.4.5. Classification and mechanisms of resistance with relevance to Saudi Arabia

The development of easily transmissible genes expressing carbapenemases is the main mechanism behind Enterobacteriaceae's resistance to carbapenems. Three different types of carbapenemases were identified depend on neculic acid sequence homology. Class A and D

carbapenemases are serine, whereas class B carbapenemases are metallo-β-lactamases (MBL) (Bush et al., 2010). Of the class A carbapenemases, Klebsiella pneumoniae carbapenemase (KPC) is the most prevalent and clinically significant; SME, IMI, and GES are less common. On the other hand, ethylenediaminetetraacetic acid (EDTA) usually inhibits Class B carbapenemases such IMP, VIM, GIM, and NDM-1 (Bush et al., 2010).

The metallo-β-lactamase NDM-1, which is relatively new, first appeared in India in 2008 and is rapidly spreading through international travel to many other countries, including Saudi Arabia (Al-Agamy et al., 2018; Yezli et al., 2017; Shibl et al., 2013). Pseudomonas aeruginosa and Acinetobacter baumannii were the first organisms to be identified as having class D carbapenemases. The occurrence of OXA-48 enzyme-encoding carbapenem-resistant Klebsiella pneumoniae has been documented in a number of Saudi Arabian studies. A tertiary care hospital in Riyadh was connected to an outbreak of multi-drug resistance, carbapenem-resistant Klebsiella pneumonia, which carries the OXA-48 gene and has mutations in outer membrane protein 36 (Zaman et al., 2014).

2.4.6. Molecular characterization of CRE reported from Saudi Arabia

According to research conducted in Saudi Arabia and the Gulf, NDM1 and OXA-48 like gene are the two commen carbapenemases responsible for resistance in Enterobacteriaceae (Zaman et al., 2014; Al-Agamy et al., 2018; El Ghany et al., 2018; Yezli et al., 2017; Alotaibi Fawzia et al., 2017; Al-Agamy et al., 2013). Other carbapenemases and isolates containing K pneumoniae carbapenemase (KPC) enzymes, like KPC-1, KPC-2, and KPC-3, are rare in Saudi Arabia and other Gulf countries.

The resistant strain of KPC had discovered to have been acquired by an elderly Saudi male patient who was admitted to the critical care unit for an extended period of time (Al-Qadheeb Nada et al., 2010). Moreover, of the 200 carbapenem-non-susceptible Enterobacteriaceae isolates collected from 16 hospitals across the Gulf, including Saudi Arabia, none included KPC-isolates (Sonnevend et al., 2015). The most often discovered carbapenemase gene, according to the same study, was bla NDM-1, followed by bla OXA-48-like gene. Three sizable clones of bla NDM-1 harboring Klebsiella pneumoniae strain ST152 were among the 22 isolates from Saudi Arabia (Sonnevend et al., 2015).

Interestingly, more than half of the isolates of OXA-48-like and NDM viruses had no prior hospitalization, travel, or foreign exposure history (Sonnevend et al., 2015). There is published data that is comparable about the molecular characteristics and resistance mechanisms of CRE in hospitals located in the Gulf region (Zowawi et al., 2013; Dortet et al., 2012; Sonnevend et

al., 2013). More significantly, endemicity and outbreaks are associated with plasmid-encoded genes carried by multi-resistant bacteria. K. pneumoniae isolates were found to co-express the OXA-48 and CTX-M-15 ESBL types during an outbreak in a tertiary care hospital in Riyadh (Zaman et al., 2014).

Zowawi et al. established the molecular characterization of CRE in hospitals throughout the Gulf area. It was discovered that six isolates coproduced the NDM and OXA-48 kinds. Of the 45 carbapenemase producers found, OXA-48 (35 isolates) and NDM (16 isolates) were the most common types. There were no KPC, VIM, or IMP producers to be discovered. In 17 isolates, neither carbapenemase activity nor carbapenemase genes were discovered. Additional resistance mechanisms, such as porin loss and ESBL production connected to a reduction in the permeability of the outer membrane, have been hypothesized (Zowawi et al., 2013).

Similar findings were noted in another study (Zaman et al., 2018), in which the OXA-48 gene alone was the most common carbapenemase detected in (67.6%) of the isolates of Klebsiella pneumoniae, followed by NDM-1 alone in (12.7%) of the isolates. Furthermore, the presence of carbapenem-resistant uro-pathogenic Escherichia coli in the population was investigated. NDM-1, NDM-5, and OXA-181 have been found to be present in ten E. Coli strains that cause urinary tract infections and are resistant to carbapenem (El Ghany et al., 2018).

Significant amounts of Extended-spectrum β-lactamase (ESBL) were discovered in the Gulf region, and the incidence of CRE infections was rising. The most prevalent genotypes are NDM-1, OXA-48, and CTX-M-15. Conversely, less common enzymes such GES-11, PER-7, and PME-1 were found (Sonnevend et al., 2015).

2.4.7. Outcomes of CRE infection

Carbapenem resistance was independently connected to 26%–44% of deaths in seven studies that used Klebsiella pneumoniae as the primary source of infection, according to a meta-analysis of nine studies on CRE infections published before 2012 (Falagas et al., 2014). Searches on PubMed provide only a small number of published clinical studies that describe the clinical characteristics and outcomes of CRE-infected patients in Saudi Arabia. Four of the nine Saudi Arabian patients died from septic shock that did not improve with medical intervention (Alotaibi Fawzia et al., 2017).

In a similar line, nine out of 29 patients (31%) with CRE infection died, as opposed to 7/58 (12.1%) of their matched controls (Garbati et al., 2016). Mortality was associated with advanced age, comorbidities, prior carbapenem use, ICU admission, mechanical ventilation, and central line insertion. The author came to the conclusion that a decreased death rate was

associated with the combination use of antibiotics (Garbati et al., 2016). Nevertheless, there are no clinical studies that offer strong support for combination therapies against CRE invasive infections as compared to colistin alone.

In a systematic review of 20 studies, bacteraemia accounted for the majority of infections in 8 of them, but the combination of tigecycline and gentamicin had the lowest mortality(50%) when compared to the combinations of tigecycline-colistin and carbapenem-colistin (64% and 67%, respectively) (Falagas Matthew et al., 2014).. Furthermore, only three studies found that combination therapies significantly reduced death when compared to monotherapy among critically ill patients with bacteraemia. Ceftazidime-avibactam, a novel combination of lactam and lactamase inhibitors, has been approved to treat of serious bacterial infections caused by organisms non suscesptable to carbapenem. Unfortunately, plasmid-borne mutations (blaKPC-3) in three K. pneumoniae isolates developed in three individuals during the course of 10 to 19 days of ceftazidime-avibactam treatment.

Development of Plasmid-Borne blaKPC-3 Mutations Leading to Ceftazidime-Avibactam Resistance in the Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infections (Shields et al., 2017). Other treatment options included fosfomycin, tigecycline, minocycline, and the more recent combination medications like plazomicin, eravacycline, imipenem-relebactam, and meropenem-vaborbactam, in addition to polymyxin and aminoglycoside (Thaden et al., 2016). In conclusion, CRE infection is a serious clinical issue with a high death rate due to the lack of an effective treatment plan and the challenge of treating strains of the virus that are usually pan-resistant.

2.4.8. Public health concerns

There are several public health concerns brought up by the emergence and spread of CRE in Saudi Arabia. First, there is the mass migration of pilgrims during the Hajj seasons, followed by the transfer of patients in need of medical attention. The second is the unchecked use of antibiotics. Third, the inadequate and inadequate waste disposal infrastructure in the western area of Saudi Arabia raises the possibility that intestinal CRE strains will find their way into drinking water sources. The growth in the prevalence of carbapenem resistance gene clones among Enterobacteriaceae species connected to community-acquired diseases, such as urinary tract infections (UTIs), is the final and fourth cause for concern.

2.5. Efficiency of CAZ-AVI within carbapenem-resistant Enterobacterales and CRKP infections

The two main antimicrobials that have been used extensively to treat of CRKP are tigecycline and Colistin. New antimicrobials, however, have just recently become accessible. It seems that

one of the most successful is ceftazidime-avibactam (CAZ-AVI) (Karampatakis et al., 2023). Karampatakis et al. reported that CAZ-AVI had superior clinical success rates against carbapenem-resistant Klebsiella pneumoniae infections in comparison to other antimicrobials. Additionally, they stated that for Carbapenem-resistant Klebsiella pneumoniae infections, CAZ-AVI shown decreased 28- and 30-day mortality rates in comparison to other antimicrobials (Karampatakis et al., 2023).

According to Zhen et al., CAZ-AVI might be a useful treatment for illnesses brought on by drug-resistant Gram-negative bacteria. CAZ-AVI needs to be used cautiously in order to maximize effectiveness and reduce the development of resistance (Zhen et al., 2022). According to Pournaras et al., the rise in colistin and tigecycline resistance in CRKP has resulted in the recent release of novel antimicrobial drugs (Pournaras et al., 2011). A new antibiotic called ceftazidime-avibactam, or CAZ-AVI, has demonstrated promise in the safe and effective treatment of CRKP strains that produce KPC and OXA-48 (Kalil et al., 2018). Ceftazidime-avibactam, also known as CAZ-AVI, is a novel β-lactam b lactamase inhibitor that has demonstrated potential against certain class D (OXA-48), class C (AmpC), and class A KPC that produce CRE in vitro (Sheu et al. 2015).

Both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the US have approved the use of CAZ-AVI in the treatment of infections for which no other therapies are available. Complex urinary tract infections, complex intraabdominal infections, and ventilator-associated pneumonia are among these infections (FDA, 2018; EMA, 2016; FDA, 2020). As a result, CAZ-AVI has been employed as a first-line medication to treat CRE infections. It has been shown that avibactam, a non-β-lactam/lactamase suicidal inhibitor, in conjunction with ceftazidime, a third-generation cephalosporin, is effective against class A, class C, and certain class D (OXA-48) K. pneumonia in both microbiological and clinical settings. carbapenemases (Abu Jaber et al., 2024).

CHAPTER III

Methodology

3.1 Research Design

The board of the institute's Research Ethics Committee approved and revised the current investigation, which is a retrospective cohort single-center study (#AFHSRMREC/2022/MICROBIOLOGY/661),WMA Declaration of Helsinki Standards of ethics was approved before starting our study . This study did not need the patients' formal informed consent because it was observational and retrospective in nature. Additionally, the experiment was approved by the Research Ethics Committee board, which waived the need for these consents. This study covered patients who were admitted to the Saudi Southern Region Armed Forces Hospitals in Khamis Mushait, Saudi Arabia between August 1, 2018, and May 1, 2023. The study provided a comparative evaluation between the two groups: In addition to normal care, patients in Group II received extra antibiotics and CAZ-AVI alone. Group I consisted of control patients who were given standard antibiotic treatment for their K. pneumonia infection, which included aminoglycoside, carbapenem, colistin, and tigecycline. During the course of 30 days, clinical outcomes were compared between the groups, accounting for all causes of mortality, clinical remission, microbiological recurrence, and eradication.
The Armed Forces Hospital in the southern region is regarded as one of the top medical facilities in the world, providing Ministry of Defense soldiers with medical and health services (diagnostic, preventative, and curative) across all medical disciplines. Serious cases are brought to this medical facility from local civilian hospitals as well as from military hospitals in Jizan, Sharurah, and Najran. For certain circumstances, it serves as a reference hospital. Over the course of four decades, hospital facilities in the southern region were developed and expanded to form the modern medically integrated monument. The hospital became an integrated hospital center for the foreseeable future when its bed capacity was increased to 571 beds.

3.2. Participants/Population and Sample

The following patients were included in this study:

1. Hospitalized patients in any department and were older than eighteen.
2. Patients who had K. pneumoniae OXA 48-like genes and were infected at any site, as confirmed by drug sensitivity and bacterial cultures.

3. Patients who received one or more antibiotic treatments beginning with positive culture results and continuing for at least five days.

The following patients were excluded from the study:

1. Patients who were younger than 18 years old
2. Patients who passed away before receiving OXA-48 antibiotic therapy or those whose use of antibiotics was too short to allow for a clinical efficacy assessment.
3. Patients who did not carry the OXA-48-like gene for K. pneumonia.

3.3 Data Collection Tools/Materials

The clinical data of the patients who were enrolled was gathered and monitored by data collection sheets until the patients were discharged or passed away. These documents included the patient's age and gender in addition to details regarding the infection site, baseline co-morbidity, laboratory results, ICU stays, prescribed antibiotics, and clinical status.

A microbiological lab technologist and two clinical pharmacists collected the data, which were then anonymized. The Armed Forces Hospital Southern Region's infectious disease experts evaluated the collected data according to three standards: microbiological eradication, clinical success, and recurrence. The following definitions were utilized in the evaluation of these results. The trial's primary endpoint was 30-day all-cause mortality, which was defined as all-cause fatalities that transpired within 30 days of obtaining bacterial isolates from infected patients (first-positive cultures for the OXA-48-like gene in CRKP patients) (Akyüz et al., 2021). The isolates from CRKP patients were identified using the minimum inhibitory concentrations (MICs) of imipenem or meropenem equal to or greater than 4 mg/L (CLSI, 2020). The trial's secondary outcomes included clinical success and indicators of antibiotic-microbiological efficiency, such as bacterial recurrence and microbial elimination.

Clinical success was defined as improvement in symptoms and signs from baseline to therapy end, including defervescence (fever remission; <38.0 °C or 100.4 °F for 48 h), normalization of WBC counts (<11.0 × 109/L), procalcitonin (≤0.05 μg/L), and/or C-reactive protein (≤3 mg/L) blood levels (Kinget al., 2017; Shirley, 2018). Microbial eradication was defined as two consecutive negative cultures obtained from the same or different locations (Tamma et al., 2023). Bacterial recurrence/relapse was defined as bacteraemia with the same species or susceptibility pattern detected in blood isolates following at least one negative microbe growth (Shirley, 2018).

3.4 Data Analysis Procedures

The statistical analyses were carried out using open-source JASP® v.0.18.3 statistical software with a dynamic update of results (University of Amsterdam, Amsterdam, The Netherlands) and GraphPad Prism® v5.01 (La Jolla, CA, USA), which were also used for the analysis and graphical representations as needed. A p-value of less than 0.05 was judged statistically significant.

Descriptive statistics (means ± standard error of means, medians with minimum-maximum ranges, and medians with interquartile ranges) were used to analyze the demographic data. Both percentages and numbers were used to present the results. The study used an independent sample t-test or a Mann-Whitney U test for data that were normally distributed or non-normally distributed, respectively, to assess which treatment arm was superior. Categorical data are analyzed by contingency testing after being reported as case numbers and percentages.

Any potential independent variables (predictors) linked to the clinical and microbiological efficacy of CAZ-AVI, including patient demographics, ICU admission, inotrope administration, infection sites, co-morbidities, specifics of antibiotic usage, clinical signs, and laboratory results, were assessed using univariate and multivariable logistic regression analyses.

3.5 Study Plan

In order to demonstrate the superiority of ceftazidime-avibactam over other antibiotics in terms of 30-day mortality, clinical remission, and microbial recurrence, we conducted a retrospective cohort single-center study evaluating two groups: the control group, which received standard antibiotic therapy for the treatment of Klebsiella pneumonia OXA 48-like infection and was considered to be an antibiotic other than ceftazidime-avibactam. This group included carbapenems, colistin, tigecycline, and aminoglycoside, either as a monotherapy or in combination regimen.

Any patient over the age of 18 who had undergone one or more antibiotic treatments and had the Klebiella pneumonia OXA 48-like gene, regardless of the source of infection, was eligible to participate in the research. Patients under the age of eighteen and those who got less than a five-day antibiotic regimen or no antibiotics at all during the infection were not included in the study.

The two sections of the data collection sheet are an appraisal based on the literature and demographic variables. A panel of experts evaluated the content validity of the data collection

sheet, which contained recovery needs and signs of CRE infection. A clinical pharmacist, a microbiologist, and an infectious disease expert were on the panel. The time frame for collecting the data was August 1, 2018, through May 1, 2023.

CHAPTER IV

Findings

4.1 Patients' Characteristics

Based on the established inclusion and exclusion criteria, the study included 114 patients with K. pneumonia OXA-48-like genes. Patients under the age of 18, those who died before receiving antibiotics, and those who used antibiotics for fewer than five days were excluded. Of these patients, 64 were given CAZ-AVI alone or in combination with standard therapy (intervention group), and 50 were given standard therapy and served as the comparative control group. Between August 1, 2018 and May 1, 2023, 228 CRKP patients were admitted to the Armed Forces Hospitals in the southern region of Khamis Mushait, Saudi Arabia.

In total, 85 (74.6%) of the included patients were admitted to the ICU for medical condition treatment; 42 (65.6%) and 43 (86.0%) of the intervention and control groups were hospitalized, respectively. Table 1 displays the demographic and baseline clinical characteristics of CRKP OXA-48-like infected patients. The median patient age was 71 years old (minimum 20.0-maximum 102.0), and the majority of patients were male (66; 57.9%). Nearly 49% of the patients received inotropes such as dopamine, epinephrine, norepinephrine, and/or vasopressin. The percentages of infection locations were as follows: 4 (3.5%) for urinary tract infections, 21 (18.4%) for soft tissues, 31 (27.2%) for respiratory tract infections, and 30 (26.3%) for bloodstream infections. K. pneumonia OXA-48-like strains caused multiple-site infections in nearly 25% of the study participants. Notably, there were 3 (6.0%) versus 18 (28.1%) fewer soft tissue infections in the control patient group than in the intervention patient group.

Numerous co-morbidities were identified in the patient population; the most common diagnoses were cardiovascular disease (72.8%), diabetes mellitus (60.5%), respiratory disease (32.5%), and renal disease (40.4%).

Co-morbidity proportions were not significantly different between the intervention and control groups ($p > 0.05$). Baseline lab tests and clinical symptoms were assessed, including fervescence (≥38.0 °C; 100.4 °F for 48 hours), white blood cell (WBC) counts, neutrophil counts, and C-reactive protein (CRP) levels. The patients' average WBC and neutrophil counts were 12.0 × 109/L (±0.7) and 12.7 × 109/L (±2.0). The control group had greater CRP levels than the intervention group, with 169.3 mg/L (±21.4) versus 80.1 mg/L (±8.7). Fever was present in 54.4% of the total examined patients, with controls accounting for a larger number of 35 (70.0%).

Table 1

Demographic features and baseline clinical characteristics of patients with OXA-48-like CRKP infections.

Variables	**Total Admitted Patients (*n* = 114)**	**Intervention (*n* = 64)**	**Control (*n* = 50)**	***p-values***
Age (years) *	71 (20.0–102.0)	75 (20.0–102.0)	69 (27.0–97.0)	0.094
Sex (Female)	48 (42.1%)	25 (39.1%)	23 (46.0%)	0.556
ICU admissions	85 (74.6%)	**42 (65.6%)**	**43 (86.0%)**	**0.017**
Inotropes **	56 (49.1%)	27 (42.2%)	29 (58.0%)	0.131
Sites of infections				
Multi-site infection ***	28 (24.6%)	11 (17.20%)	17 (34.0%)	0.663
Bloodstream	30 (26.3%)	18 (28.1%)	12 (24.0%)	0.053
Respiratory tract	31 (27.2%)	14 (21.9%)	17 (34.0%)	1.000
Soft tissues	21 (18.4%)	**18 (28.1%)**	**3 (6.0%)**	**0.003**
Urinary tract	4 (3.5%)	3 (4.7%)	1 (2.0%)	0.318
Co-morbidities				
Respiratory diseases	37 (32.5%)	20 (31.3%)	17 (34.0%)	0.841
Cardiovascular diseases	83 (72.8%)	46 (71.9%)	37 (74.0%)	0.835
Diabetes mellitus	69 (60.5%)	40 (62.5%)	29 (58.0%)	0.701
Kidney diseases	46 (40.4%)	26 (40.6%)	20 (40.0%)	1.000
Central nervous system diseases	16 (14.0%)	8 (12.5%)	8 (16.0%)	0.594
Cerebrovascular diseases	23 (20.2%)	10 (15.6%)	13 (26.0%)	0.240
Gastrointestinal diseases	5 (4.4%)	3 (4.7%)	2 (4.0%)	1.000
Septic shock/sepsis	29 (25.4%)	15 (23.4%)	14 (28.0%)	0.666
Tumors	2 (1.7%)	1 (1.6%)	1 (2.0%)	1.000
COVID-19 infections	21 (18.4%)	13 (20.3%)	8 (16.0%)	0.631
Antibiotic usage				
Duration time of treatment (days) *	14.0 (±0.7)	14.2 (±1.0)	13.7 (±0.9)	0.881
Monotherapy	24 (21.1%)	13 (20.3%)	11 (22.0%)	0.825
Combinations of two agents	49 (43.0%)	28 (43.8%)	21 (42.0%)	1.000

Combinations of ≥triple agents	41 (36.0%)	23 (35.9%)	18 (36.0%)	1.000
Aminoglycosides	9 (7.9%)	6 (9.4%)	3 (6.0%)	0.729
Aztreonam	4 (3.5%)	3 (4.7%)	1 (2.0%)	0.630
Colistin	61 (53.5%)	32 (50.0%)	29 (58.0%)	0.452
Meropenem	56 (49.1%)	**8 (12.5%)**	**48 (96.0%)**	**<0.0001**
Tigecycline	45 (39.5%)	23 (35.9%)	22 (44.0%)	0.442
Lab and clinical signs				
WBC counts ($\times 10^9$/L) *	12.0 (±0.7)	11.3 (±0.7)	13.0 (±1.2)	0.355
Neutrophil counts ($\times 10^9$/L) *	12.7 (±2.0)	12.7 (±2.1)	12.6 (±1.9)	0.261
C-reactive protein (mg/L) *	121.0 (±11.7)	**80.1 (±8.7)**	**169.3 (±21.4)**	**0.0011**
Fervescence ****	62 (54.4%)	**27 (42.2%)**	**35 (70.0%)**	**0.004**

Otherwise undefined, data are represented as case numbers and their percentages out of total. * Data representation as per median (minimum–maximum) or mean (± standard error of mean). ** Inotropes were administered vasoactive agents including dopamine, epinephrine, norepinephrine, and/or vasopressin. *** Multi-site infections; infections via the OXA-48-like CRKP strain at more than one site. **** Temperatures of 38.0 °C (100.4 °F) or above for 48 h were considered fever. *p*-values were estimated using a *t*-test, Mann–Whitney U test, or contingency testing (Chi-square or Fisher's exact test) based on the data. Values in bold represent statistical significance ($p < 0.05$).

4.2 Antibiotic Medications

In the end, patients with CRKP OXA-48-like infections received antibiotics for an average of 14.0 (±0.7) days, beginning with the first positive cultures for the OXA-48-like gene (Figure 1A). Antibiotics were administered as monotherapy in 24 (21.1%) of all patient instances, or as a combination of two or more medications in 49 (43.0%) and 41 (36.0%) of the total examined patients, respectively (Figure 1B).

Standard antibiotic regimens comprised aminoglycosides for 9 (7.9%), aztreonam for 4 (3.5%), colistin for 61 (53.5%), and tigecycline for 45 (39.5%) of the total number of cases. All routine antibiotics were statistically indifferent between the intervention and control groups, with the exception of meropenem, which was administered more frequently (48; 96.0%) in practically all cases in the compared patient group (Figure 1C).

For 13 (21.9%), 28 (43.8%), and 23 (35.9%) of the intervention patient cases, respectively, the CAZ-AVI medication was administered as definitive therapy rather than empirically (starting with first-positive cultures for the OXA-48-like gene). It could be used alone as monotherapy, in combination with one other drug, or even in combination with more than one drug (Figure 1D).

The percentages of the added antibiotic type to CAZ-AVI are as follows: of the intervention group instances, 6 (9.4%) had aminoglycosides, 3 (4.7%) had aztreonam, 32 (50.0%) had colistin, 8 (12.5%) had meropenem, and 23 (35.9%) had tigecycline (Figure 1E). As a result, greater frequencies were shown for the usual antibiotic therapy of colistin and tigecycline in conjunction with CAZ-AVI.

A dose of 940 mg to 2500 mg of administered CAZ-AVI was given once a day (q24h), every other day (EOD), twice a day (q12h), or even three times a day (q8h). The normal dosage of 2500 mg every eight hours was reserved for patients who were admitted and had a creatinine clearance (CrCl) of more than 50 mL/min; however, it was discovered that CAZ-AVI dosing was in compliance with clinical recommendations and practices based on the patients' physiological status. Patients were given 1250 mg (q8h) if their reported CrCl was greater than 30-to-50 mL/min. CAZ-AVI was reported to be administered at the same dose every 24 hours (q24h) to patients with reported CrCl> 5–15 mL/min, while patients with reported CrCl> 15–30 mL/min got 940 mg q12h. In patients with CrCl ≤ 5 mL/min, a dose of 940 mg EOD was reported; on prolonged intermittent renal replacement therapy (PIRRT) days, critically sick patients with acute kidney injury received 1250 mg q12h CAZ-AVI. Interestingly, the average initial CAZ-AVI dosage for all treated patients was 1.25 g, and the total dosage for the course of the antibiotic was 39.74 g, with a daily average of 3.75 g (Figure 1F).

Based on the physiological status of the patients, the most commonly seen CAZ-AVI dose regimen was 2500 mg every 8 hours, followed by 940 mg every 12 hours. The least common dose regimen, with 27 (42.19%), 17 (26.56%), and 2 (3.13%) patient cases, was 1250 mg every 12 hours (Figure 1G).

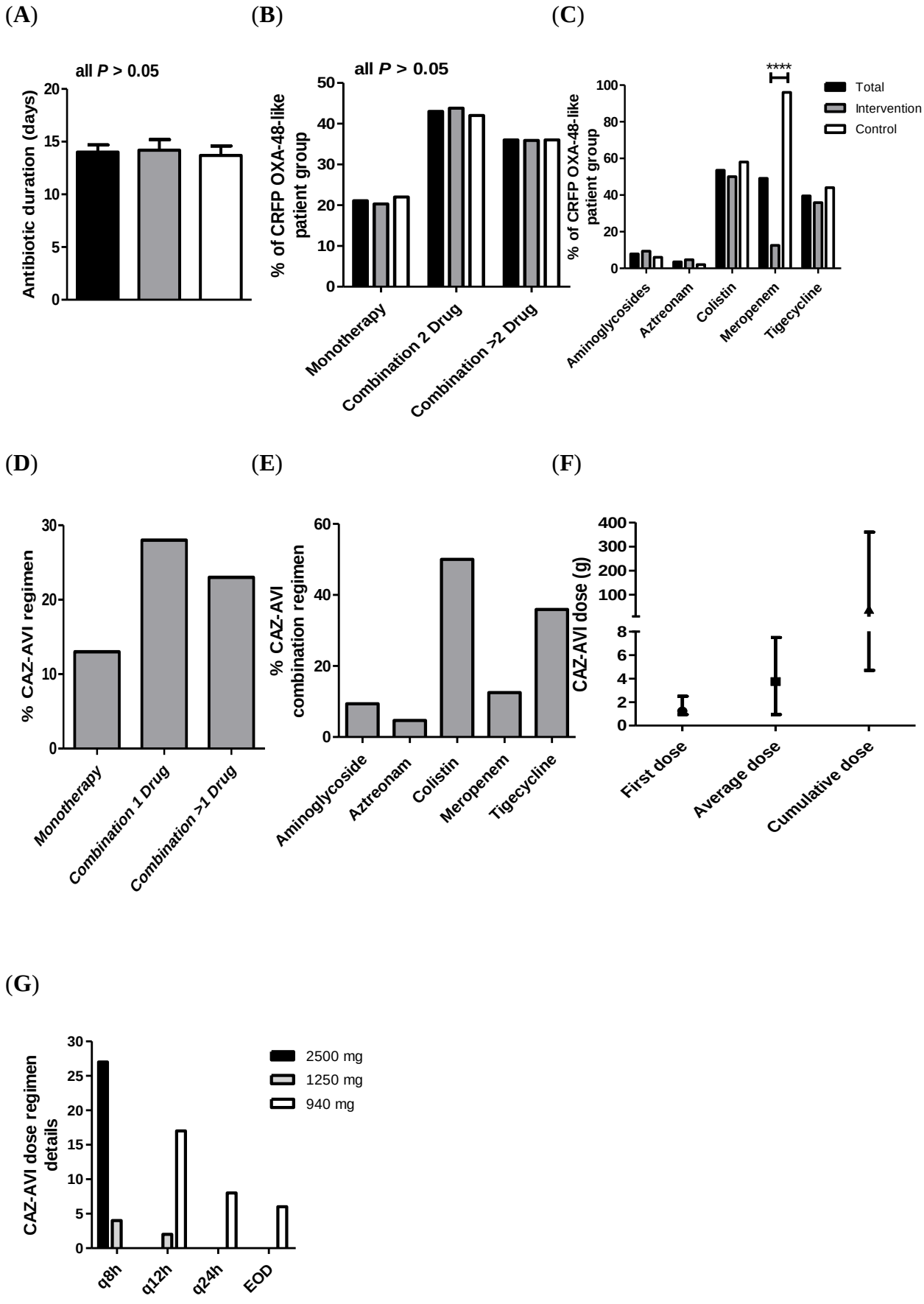

(A)
(B)
(C)
all P > 0.05
Antibiotic duration (days)
all P > 0.05
% of CRFP OXA-48-like patient group
Monotherapy
Combination 2 Drug
Combination >2 Drug
****
Total
Intervention
Control
Aminoglycosides
Aztreonam
Colistin
Meropenem
Tigecycline
(D)
(E)
(F)
% CAZ-AVI regimen
Monotherapy
Combination 1 Drug
Combination >1 Drug
% CAZ-AVI combination regimen
Aminoglycoside
Aztreonam
Colistin
Meropenem
Tigecycline
CAZ-AVI dose (g)
First dose
Average dose
Cumulative dose
(G)
CAZ-AVI dose regimen details
2500 mg
1250 mg
940 mg
q8h
q12h
q24h
EOD

Figure 4

Antibiotic drug usage within CRKP OXA-48-like patients. (**A**) Antibiotic duration of treatment in days. (**B**) Antibiotic sole and combination regimens. (**C**) Percentages of antibiotic members across total, intervention, and control patient groups. (**D**) CAZ-AVI sole and combination regimens in intervention patients. (**E**) Percentages of CAZ-AVI combined with antibiotic members of the standard therapy. (**F**) Dose regimen details of CAZ-AVI usage (median with maximum and minimum ranges). (**G**) Frequency of the CAZ-AVI dose regimen as per patients' physiological status. Comparative antibiotic data between intervention versus the control groups were statistically insignificant for almost all items (*p-values*> 0.05). **** $p < 0.0001$.

4.3 Parameters Associated with CAZ-AVI Clinical and Microbiological Outcomes

After the study was analysed, 31 patients in the intervention group—51.6% of the total patients—had 30-day all-cause mortality. In contrast, 66% of patients in the control group passed away from any cause within 30 days of the bacterial isolation (Akyüz and Korkmaz, 2021).

Of the 64 intervention patients, 27 (42.0%) had clinical success with fever remission together with WBCs, procalcitonin, and CRP blood level normalization, according to the accepted definitions of patients' secondary outcomes (King et al., 2017; Shirley, 2018).

However, in the comparator group, 11 patients over 50 (22.0%) achieved the same defined clinical success. In terms of microbial eradication, 21 control patients (42.0%) had microbial eradication, whereas 44 CAV-AVI patients (68.0%) had microbial eradication, demonstrating two consecutive negative cultures from the same and distinct sites.

Following at least one negative microbe growth, only 5 (7.8%) patients in the CAV-AVI administered group and 12 (24%) patients in the comparator group experienced bacterial recurrence, exhibiting bacteraemia with the same species and susceptibility pattern as the index blood isolate (Shirley, 2018). Notably, at p-values < 0.05, the study's findings revealed statistically significant differences in the clinical and microbiological outcomes of patients between the intervention and comparison groups (Table 2).

Analyzing the data in relation to antibiotic regimens (add-on therapy and monotherapy) has produced some intriguing results. Clinical success (46.2% versus 27.3%) and 30-day all-cause mortality (69.2% versus 54.5%) were higher case percentages under monotherapy settings for

OXA-48-like CRKP patients treated with CAZ-AVI than for patients receiving conventional therapy.

In addition, compared to the matching conventional therapy, the intervention CAZ-AVI monotherapy showed microbiological outcomes at higher case percentages for microbial eradication (68.8% versus 42.0%) and lower ones for bacterial recurrences (7.8% against 24.0%).

However, statistical examination of the presented differential outcomes revealed no significant differences ($p > 0.05$) between the control group receiving monotherapy and the intervention group. Conversely, in OXA-48-like CRKP cases receiving CAZ-AVI as an adjuvant to normal therapy, statistically significant differences were shown in both the clinical and microbiological results. Since only 23 patients died from the first therapy, CAZ-AVI add-on therapy was associated with lower 30-day all-cause death rates (45.1%) compared to the controls (74.4%; $p = 0.009$).

For the CAZ-AVI add-on group, clinical success was statistically significant at higher rates, reaching 41.2% ($p = 0.043$), with 21 patients showing fever remission and WBC/C-reactive protein normalization, compared to only 8 patients. Patients who received CAZ-AVI add-on therapy had nearly 1.5 times greater microbiological results (microbial eradication) than patients who only got conventional therapy (66.7% versus 43.6%; $p = 0.034$).

The most intriguing finding was that the control patients had nearly seven times the rate of bacterial recurrences (20.5%) compared to the CAZ-AVI add-on therapy recipients (3.9%), with a p-value of 0.018.

Table 2

Clinical and microbiological outcomes of patients with OXA-48-like CRKP infections.

Outcomes *	**Total Admitted Patients (*n* = 114)**	**Intervention (*n* = 64)**	**Control (*n* = 50)**	***p*-Values**
Clinical success	38 (33.3%)	27 (42.2%)	11 (22.0%)	**0.028**
Microbial eradication	65 (57.0%)	44 (68.8%)	21 (42.0%)	**0.007**
Bacterial recurrence	17 (14.9%)	5 (7.8%)	12 (24.0%)	**0.019**

30-day all-cause mortality	67 (58.7%)	32 (50.0%)	35 (70.0%)	**0.036**
	Total	**Intervention**	**Control**	
	Monotherapy patients (*n* = 24)	**Monotherapy (*n* = 13)**	**Monotherapy (*n* = 11)**	***p*-values**
Clinical success	9 (37.5%)	6 (46.2%)	3 (27.3%)	0.423
Microbial eradication	14 (58.3%)	10 (76.9%)	4 (36.4%)	0.095
Bacterial recurrence	7 (29.2%)	3 (23.1%)	4 (36.4%)	0.659
30-day all-cause mortality	15 (62.5%)	9 (69.2%)	6 (54.5%)	0.675
	Total	**Intervention**	**Control**	
	Combined therapy patients (*n* = 90)	**Add-on therapy (*n* = 51)**	**Combined therapy (*n* = 39)**	***p-values***
Clinical success	29 (32.2%)	21 (41.2%)	8 (20.5%)	**0.043**
Microbial eradication	51 (56.7%)	34 (66.7%)	17 (43.6%)	**0.034**
Bacterial recurrence	10 (11.11%)	2 (3.9%)	8 (20.5%)	**0.018**
30-day all-cause mortality	52 (57.8%)	23 (45.1%)	29 (74.4%)	**0.009**

Data are represented as case numbers and their percentages out of the total or respective patient group. ***** Bacterial recurrence = bacteremia with the same species and susceptibility pattern as the index blood isolate, following at least one negative microbe growth. Clinical success = fever remission, plus normalization of WBC count, procalcitonin, and C-reactive protein. Microbial eradication = two consecutive negative cultures from the same and different sites. The 30-day all-cause mortality = any cause of death that happened within 30 days of bacterial isolates. p-values were estimated through contingency testing (Chi-square or Fisher's exact test) based on the data. Values in bold represent statistical significance ($p < 0.05$).

4.3.1 Clinical Efficiency in CAZ-AVI Patient Group

There are notable disparities between the clinically successful and failed patients in the intervention group when comparing their demographics, patient features, and use of CAZ-AVI. Compared to patients in the treatment failure group, those who received CAZ-AVI effectively had lower percentages of female patients, fewer ICU admissions, fewer inotrope administrations, lower average WBC—neutrophil—CRP values, and fewer fever presentations ($p < 0.05$).

In contrast, compared to the therapy failure group, the same patients who had successful treatment had much greater rates of soft tissue infections and used CAZ-AVI more frequently, resulting in larger cumulative dosages and longer antibiotic duration (Table 3).

The results for CAZ-AVI patients who died compared to those who survived are fairly similar to the previously mentioned clinically successful/failure groups. Female gender, ICU stays, inotrope administrations, sepsis comorbidity, and WBC—neutrophil—CRP counts were among the variables where the values of the survivors were statistically lower than those of the survivors. However, compared to the patients who passed away, the survivors had greater rates of soft tissue infection sites and cumulative CAZ-AVI doses (Table 3).

Table 3

Variables and risk factor analysis for clinical success/efficacy and 30 day all cause mortality of CAZ-AVI-driven antibiotic regimens within CRKP OXA-48-like infected patients.

Variables	**Clinical Efficiency**			**30-Day All-Cause Mortality**		
	CAZ-AVI Treatment Success (*n* = 27)	**CAZ-AVI Treatment Failure (*n* = 37)**	***p-values***	**CAZ-AVI Patient Survived (*n* = 32)**	**CAZ-AVI Patient Deceased (*n* = 32)**	***p-values***
Age (years) *	71 (27.0–97.0)	67 (31.0–93.0)	0.960	69 (27.0–97.0)	70 (39.0–95.0)	0.333
Sex (Female)	**7 (25.9%)**	**18 (48.6%)**	**0.026**	**8 (25.0%)**	**17 (53.1%)**	**0.039**
ICU admissions	**13 (48.1%)**	**29 (78.4%)**	**0.017**	**14 (43.8%)**	**28 (87.5%)**	**0.017**
Inotropes	**4 (14.8%)**	**23 (62.2%)**	**< 0.001**	**4 (12.5%)**	**23 (71.9%)**	**< 0.0001**
Sites of infections						
Multi-site infection	5 (18.5%)	6 (16.2%)	1.000	7 (21.9%)	4 (12.5%)	0.509
Bloodstream	6 (22.2%)	12 (32.4%)	0.413	8 (25%)	10 (31.3%)	0.782
Respiratory tract	5 (18.5%)	9 (24.3%)	0.761	6 (18.8%)	8 (25.0%)	0.763
Soft tissues	**12 (44.4%)**	**6 (16.2%)**	**0.023**	**13 (40.6%)**	**5 (15.6%)**	**0.049**
Urinary tract	1 (3.7%)	2 (5.4%)	1.000	0 (0.0%)	3 (9.4%)	0.238
Co-morbidities						
Respiratory diseases	8 (29.6%)	12 (32.4%)	1.000	8 (25.0%)	12 (37.5%)	0.419
Cardiovascular diseases	21 (77.8%)	25 (67.6%)	0.413	22 (68.8%)	24 (75.0%)	0.782

Diabetes mellitus	17 (63.0%)	23 (62.1%)	1.000	18 (56.3%)	22 (68.8%)	0.439
Kidney diseases	11 (40.7%)	15 (40.5%)	1.000	12 (37.5%)	14 (43.75%)	0.799
Central nervous system diseases	3 (11.1%)	5 (13.5%)	1.000	4 (12.5%)	4 (12.5%)	1.000
Cerebrovascular diseases	4 (14.8%)	6 (16.2%)	1.000	4 (12.5%)	6 (18.8%)	0.732
Gastrointestinal diseases	1 (3.7%)	2 (5.4%)	1.000	1 (3.1%)	2 (6.3%)	1.000
Septic shock/sepsis	4 (14.8%)	11 (29.7%)	0.235	**3 (9.4%)**	**12 (37.5%)**	**0.016**
Tumors	0 (0.0%)	1 (2.7%)	1.000	0 (0.0%)	1 (3.1%)	1.000
COVID-19 infections	5 (18.5%)	8 (21.6%)	1.000	3 (9.4%)	10 (31.3%)	0.060
Antibiotic usage						
CAZ-AVI duration therapy (days)*	**16.8 (±1.7)**	**11.6 (±1.0)**	**0.003**	16.1 (±1.6)	11.4 (±0.8)	0.037
CAZ-AVI monotherapy	6 (22.2%)	7 (18.9%)	0.763	5 (15.6%)	8 (25%)	0.536
Combinations of two agents	13 (48.1%)	15 (40.5%)	0.615	16 (50.0%)	12 (37.5%)	0.450
Combinations of ≥ triple agents	10 (37.0%)	13 (35.1%)	1.000	13 (40.6%)	10 (31.3%)	0.603
Aminoglycosides	2 (7.4%)	4 (10.8%)	1.000	5 (15.6%)	1 (3.1%)	0.105
Aztreonam	1 (3.7%)	2 (5.4%)	1.000	1 (3.1%)	2 (6.3%)	1.000
Colistin	13 (50.0%)	19 (51.4%)	1.000	14 (43.8%)	18 (56.3%)	0.454
Meropenem	3 (48.1%)	5 (13.5%)	1.000	5 (15.6%)	3 (9.4%)	0.708
Tigecycline	12 (44.4%)	11 (29.7%)	0.294	11 (34.4%)	12 (37.5%)	1.000
CAZ-AVI first dosage (g)	2.5 (0.94–2.5)	0.94 (0.94–2.5)	0.223	2.5 (0.94–2.5)	0.94 (0.94–2.5)	0.023
CAZ-AVI average dosage (g/day)	4.4 (1.9–7.5)	2.2 (0.94–7.5)	0.100	7.5 (0.94–7.5)	2.2 (0.94–7.5)	0.016
CAZ-AVI cumulative dosage (g)	**60.0 (9.4–360.0)**	**37.1 (4.7–157.5)**	**0.002**	**66.7 (6.6–360.0)**	**29.7 (4.7–157.5)**	**< 0.001**
Lab and clinical signs						
WBC counts (x 10^9/L) *	**7.6 (±0.5)**	**13.5 (±1.2)**	**< 0.001**	**8.5 (±0.7)**	**13.1 (±1.3)**	**0.016**
Neutrophil counts (x 10^9/L) *	**7.12 (±2.1)**	**15.0 (±2.9)**	**< 0.001**	**9.2 (±2.1)**	**13.3 (±2.7)**	**0.007**
C-reactive protein (mg/L) *	**25.1 (±5.6)**	**112.0 (±9.7)**	**< 0.0001**	**47.5 (±9.4)**	**108.2 (±11.5)**	**< 0.0001**

Fervescence	**2 (7.4%)**	**25 (67.6%)**	**< 0.0001**	**4 (12.5%)**	**23 (71.9%)**	**< 0.0001**

Otherwise undefined, data are represented as case numbers and their percentages out of total. * Data representation as per median (minimum–maximum) or mean (±standard error of mean). *p*-values were estimated through a *t*-test, Mann–Whitney U test, or contingency testing (Chi-square or Fisher's exact test) based on the data. Values in bold represent statistical significance ($p < 0.05$).

4.3.2 Microbiological Efficiency in CAZ-AVI Patient Group

In order to distinguish patients who demonstrated a clearance of the CRKP OXA-48-like strain from those who did not (microbial eradication versus persisting CAZ-UVI patients), a univariate analysis was also conducted for patient characteristics, demography, and CAZ-AVI usage. CRKP OX-48-like strain microbiological cultures were still positive in patients with greater percentages of female patients, inotropes receival, WBC, neutrophil, and CRP counts, fever episodes, and COVID-19 comorbidity.

On the other hand, after a course of CAZ-AVI treatment, CRKP OXA-48-like clearance was substantially correlated with increased rates of soft tissue infection sites and ICU admissions for treatment (Table 4).

In addition, these patients who had their microbes destroyed were given larger cumulative dosages of CAZ-AVI and more inotropes than the group that had microbes persisting. Lastly, compared to patients whose bacteremia had cleared up, WBC and CRP blood counts were not substantially lower in cases of bacterial relapse in CAZ-AVI patients (Table 4).

Table 4

Variables and risk factor analysis for microbial eradication and bacterial recurrence/relapse of CAZ-AVI-driven antibiotic regimens within CRKP OXA-48-like infected patients.

Variables	**Microbial eradication**			**Bacterial recurrence**		
	CAZ-AVI Infection Eradicated (*n* = 44)	**CAZ-AVI Infection Persistent (*n* = 20)**	***p-values***	**CAZ-AV Infection Relapsed (*n* = 5)**	**CAZ-AVI Infection Receded (*n* = 59)**	***p-values***

Age (years) *	69 (27.0–97.0)	70 (39.0–95.0)	0.300	69 (49.0–77.0)	70 (27.0–97.0)	0.582
Sex (Female)	**8 (18.2%)**	**17 (85.0%)**	**0.011**	0 (0.0%)	25 (42.4%)	0.147
ICU admissions	**24 (54.5%)**	**18 (90.0%)**	**0.009**	2 (40.0%)	40 (67.8%)	0.329
Inotropes	**11 (25.0%)**	**16 (80.0%)**	**< 0.0001**	0 (0.0%)	27 (45.8%)	0.068
Sites of infections						
Multi-site infection	8 (18.2%)	3 (15.0%)	1.000	2 (40.0%)	9 (15.3%)	0.201
Bloodstream	10 (22.7%)	8 (40.0%)	0.230	2 (40.0%)	16 (27.1%)	0.615
Respiratory tract	10 (22.7%)	4 (20.0%)	1.000	1 (20.0%)	13 (22.0%)	1.000
Soft tissues	15 (34.1%)	3 (15.0%)	0.143	0 (0.0%)	18 (30.5%)	0.310
Urinary tract	2 (4.5%)	1 (5.0%)	1.000	0 (0.0%)	3 (5.1%)	1.000
Co-morbidities						
Respiratory diseases	**10 (22.7%)**	**10 (50.0%)**	**0.042**	0 (0.0%)	20 (33.9%)	0.314
Cardiovascular diseases	32 (72.7%)	14 (70.0%)	1.000	4 (80.0%)	42 (71.2%)	1.000
Diabetes mellitus	29 (65.9%)	11 (55.0%)	0.419	2 (40.0%)	38 (64.4%)	0.355
Kidney diseases	17 (38.6%)	9 (45.0%)	0.784	2 (40.0%)	24 (40.7%)	1.000
Central nervous system diseases	6 (13.6%)	2 (10.0%)	1.000	1 (20.0%)	7 (11.9%)	0.499
Cerebrovascular diseases	7 (15.9%)	3 (15.0%)	0.728	1 (20.0%)	9 (15.3%)	1.000
Gastrointestinal diseases	1 (2.3%)	2 (10.0%)	0.228	0 (0.0%)	3 (5.1%)	1.000
Septic shock/sepsis	7 (15.9%)	8 (40.0%)	0.207	0 (0.0%)	15 (25.4%)	0.329
Tumors	0 (0.0%)	1 (5.0%)	0.313	0 (0.0%)	1 (1.7%)	1.000
COVID-19 infections	**4 (9.1%)**	**9 (45.0%)**	**0.002**	0 (0.0%)	13 (22.0%)	0.574
Antibiotic usage						
CAZ-AVI duration therapy (days) *	**16.0 (±1.2)**	**8.7 (±0.8)**	**< 0.0001**	17.4 (±2.5)	13.4 (±1.0)	0.100
CAZ-AVI Monotherapy	10 (22.7%)	3 (15.0%)	0.739	0 (0.0%)	13 (22.0%)	0.574
Combinations of two agents	20 (45.5%)	8 (40.0%)	0.789	4 (80.0%)	24 (40.7%)	0.159
Combinations of ≥triple agents	15 (34.1%)	8 (40.0%)	0.780	1 (20.0%)	22 (37.3%)	0.646
Aminoglycosides	5 (11.4%)	1 (5.0%)	0.656	1 (20.0%)	5 (8.5%)	0.399

Aztreonam	1 (2.3%)	2 (10.0%)	0.228	0 (0.0%)	3 (5.1%)	1.000
Colistin	21 (47.7%)	11 (55.0%)	0.788	3 (60.0%)	29 (49.2%)	1.000
Meropenem	6 (13.6%)	2 (10.0%)	1.000	0 (0.0%)	8 (13.6%)	1.000
Tigecycline	16 (36.4%)	7 (35.0%)	1.000	2 (40.0%)	21 (35.6%)	1.000
CAZ-AVI first dosage (g)	1.25 (0.94–2.5)	0.94 (0.94–2.5)	0.217	2.5 (0.94–2.5)	1.25 (0.94–2.5)	0.346
CAZ-AVI average dosage (g/day)	3.8 (0.94–7.5)	2.2 (0.94–7.5)	0.133	5.0 (1.9–7.5)	3.8 (0.94–7.5)	0.434
CAZ-AVI cumulative dosage (g)	**54.4 (6.1–360.0)**	**19.4 (4.7–127.5)**	**< 0.001**	105.0 (18.8–127.5)	39.5 (4.7–360.0)	0.080
Lab and clinical signs						
WBC counts ($\times 10^9$/L) *	**8.2 (±0.5)**	**16.5 (±1.6)**	**< 0.0001**	7.1 (±0.7)	11.1 (±0.8)	0.154
Neutrophil counts ($\times 10^9$/L) *	**8.0 (±1.8)**	**18.2 (±4.0)**	**< 0.0001**	**3.9 (±0.7)**	**11.9 (±2.0)**	**0.035**
C-reactive protein (mg/L) *	**59.8 (±9.8)**	**114.3 (±11.7)**	**< 0.001**	**21.1 (±9.6)**	**80.9 (±8.7)**	**0.025**
Fervescence	**9 (20.5%)**	**18 (90.0%)**	**0.017**	1 (20.0%)	26 (44.1%)	0.387

The independent determinants and covariates (predictors) linked to risk or protective factors for the clinical and microbiological outcomes of CAZ-AVI-based therapy were then identified by additional analysis using multivariate logistic regression. With corresponding odds ratios (ORs) of 0.105, 0.141, and 0.080, sex (percentage of female patients), ICU admission, and fever were found to be independently linked with patient mortality and to be detrimental factors for improving patient survival (Table 5).

With adjusted odds ratios of 0.004, 0.987, and 0.051, respectively, a multivariate logistic regression analysis further validated that patient fever experiences, CRP levels, and inotropes were the significant independent negative factors (risk factors) that could affect the CAZ-AVI clinical efficiency. The only clinical efficiency that was positively correlated with ICU admission (OR = 21.183) was clinical efficiency. In terms of microbiological eradication, the length of the CAZ-AVI treatment had a favorable impact on the CRKP OXA-48-like strain's clearance (OR = 1.446).

Conversely, it was shown that WBC counts and fever episodes were significant, independent covariates/factors that adversely affected the elimination of microorganisms (ORs = 0.747 and 0.013, respectively). It's interesting to note that throughout the multivariate logistic regression analysis, one factor remained constant while the effects of neutrophil counts and CRP bio levels were shown as significant, independent covariates for bacterial relapse. Figure 2 shows conditional estimation/prediction plots at respective 95% confidence intervals that highlight associations between significant independent factors/covariates and each clinical and microbiological outcome.

The risk of multicollinearity among the independent variables (predictors) was assessed in order to guarantee the accuracy of the multivariable logistic regression analysis that was performed.

According to Marcoulides and Raykov (2019) and Yoo et al. (2014), multicollinearity can reduce the regression model's statistical power by resulting in estimation coefficients and p-values that are extremely sensitive to even slight model modifications. To verify the multicollinearity assumption, it was decided to estimate the variance inflation factors (VIFs) and tolerance indices (TIs) for each independent predictor in the model.

Generally speaking, VIFs of unity (i.e., 1) and tolerance > 0.1 indicate low correlations between independent variables, whereas VIFs values less than 5 and tolerance > 0.2 indicate moderate correlations but do not require remedial action. However, the assumptions regarding critical multicollinearity levels are substantially broken for VIFs greater than 10 and tolerance less than 0.1 (Marcoulides and Raykov, 2019; Goss-Sampson, 2018).

All of the accepted regression models had VIFs for independent variables that were less than 3.5 and, on average, had high tolerance indices of >0.6 (Table 5). This indicated a good estimation of coefficients with unquestionable p-values.

Table 5

Multivariate logistic regression analysis of clinical and microbiological outcomes within CAZ-AVI-treated CRKP OXA-48-like infected patients.

Variables *	**30-Day All-Cause Mortality**	**Clinical Efficiency**

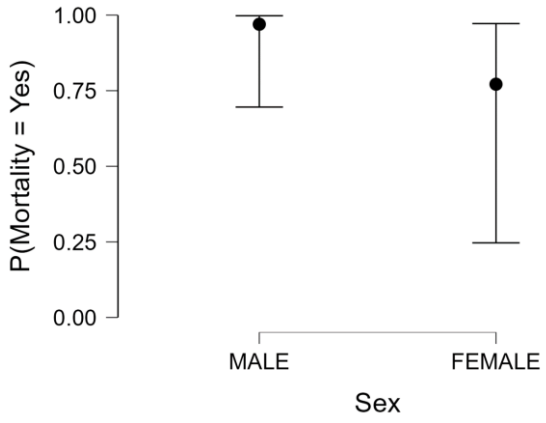
	B	**ORs (95% CI)**	***p*-Values**	**VIF (TI)**	**B**	**ORs (95% CI)**	***p*-Values**	**VIF (TI)**
Sex	**−2.252**	**0.105 (–4.200; −0.305)**	**0.023**	**1.78 (0.56)**	−1.598	0.202 (–4.229; 1.033)	0.234	1.95 (0.51)
ICU admissions	**−1.957**	**0.141 (–3.518; −0.397)**	**0.014**	**1.45 (0.69)**	**3.053**	**21.183 (–0.102; 6.208)**	**0.048**	**3.13 (0.32)**
Inotropes	−0.801	0.449 (–2.827; 1.223)	0.438	1.92 (0.52)	**−2.974**	**0.051 (–4.795; −1.153)**	**0.001**	**1.91 (0.53)**
Soft tissues	0.002	1.002 (–2.166; 2.169)	0.999	1.73 (0.58)				
Septic shock/sepsis	−0.750	0.473 (–2.970; 1.470)	0.508	1.55 (0.65)				
CAZ-AVI duration					0.049	0.952 (–0.219; 0.121)	0.572	1.70 (0.59)
CAZ-AVI cumulative	0.005	1.005 (–0.013; 0.024)	0.563	1.31 (0.77)	0.008	1.008 (–0.020; 0.036)	0.583	1.93 (0.52)
WBC counts	0.005	1.005 (–0.164; 0.175)	0.951	1.52 (0.66)	−0.235	0.790 (–0.564; 0.093)	0.160	1.73 (0.58)
Neutrophil counts	0.030	1.031 (–0.025; 0.085)	0.282	1.27 (0.79)	−0.020	0.981 (–0.125; 0.086)	0.715	1.33 (0.75)
C-reactive protein	−0.002	0.998 (–0.016; 0.012)	0.766	1.85 (0.54)	**−0.013**	**0.987 (–0.026; −0.000)**	**0.043**	**1.81 (0.55)**
Fervescence	**−2.524**	**0.080 (–4.465; −0.582)**	**0.011**	**1.70 (0.59)**	**−5.596**	**0.004 (–9.507; −1.685)**	**0.004**	**2.46 (0.41)**
Variables *	**Microbial eradication**				**Bacterial recurrence**			
	B	**ORs (95% CI)**	***p-values***	**VIF (TI)**	**B**	**ORs (95% CI)**	***p-values***	**VIF (TI)**
Sex	−2.866	0.057 (–6.318; 0.586)	0.104	3.50 (0.29)				
ICU admissions	−1.952	0.142 (–4.441; 0.536)	0.124	1.08 (0.93)				
Inotropes	−1.620	0.198 (–3.434; 0.195)	0.080	1.36 (0.74)				
Respiratory diseases	1.373	3.949 (–0989; 3.736)	0.255	1.56 (0.64)				

COVID-19 infections	0.476	1.609 (–2.066; 3.018)	0.714	1.47 (0.68)				
CAZ-AVI duration	**0.368**	**1.446 (0.101; 0.636)**	**0.007**	**1.26 (0.79)**				
CAZ-AVI cumulative	0.002	1.002 (–0.028; 0.031)	0.920	1.32 (0.76)				
WBC counts	**−0.292**	**0.747 (–0.563; −0.021)**	**0.034**	**1.48 (0.67)**				
Neutrophil counts	−0.004	0.996 (–0.063; 0.055)	0.903	1.34 (0.75)	−0.298	0.742 (–0.842; 0.247)	0.284	1.05 (0.95)
C-reactive protein	−0.004	0.996 (–0.018; 0.010)	0.598	1.09 (0.92)	−0.022	0.978 (–0.060; 0.016)	0.257	1.05 (0.95)
Fervescence	−**4.353**	**0.013 (–7.499; −1.206)**	**0.007**	**2.75 (0.36)**				

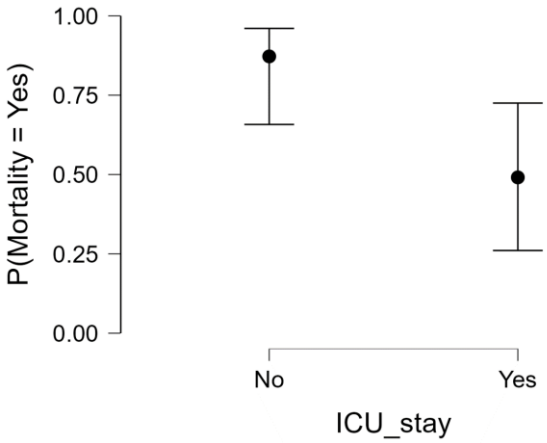
* Only variables depicted significance ($p < 0.05$) throughout the univariate analysis were included within the multivariate logistic regression analysis. B = regression coefficient; ORs = odds ratios; CI = confidence intervals. Values in bold represent statistical significance ($p < 0.05$).

Associations between significant independent factors/covariates and each clinical and microbiological outcome are illustrated via conditional estimation/prediction plots at their respective 95% confidence intervals within Figure 2.

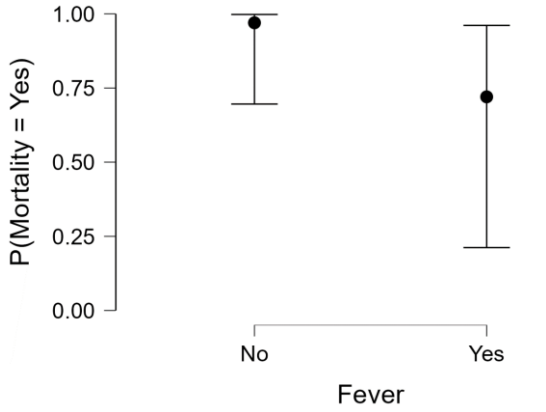
(A)


1.00
0.75
0.50
0.25
0.00
P(Mortality = Yes)
MALE
FEMALE
Sex

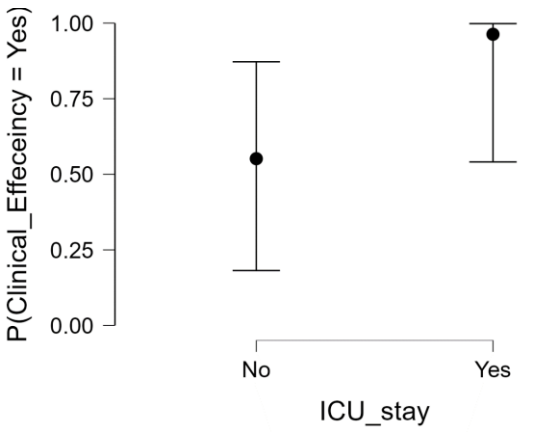
(B)


1.00
0.75
0.50
0.25
0.00
P(Mortality = Yes)
No
Yes
ICU_stay

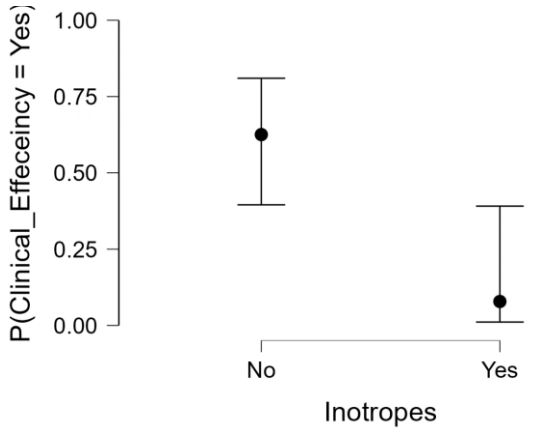
(C)


1.00
0.75
0.50
0.25
0.00
P(Mortality = Yes)
No
Yes
Fever

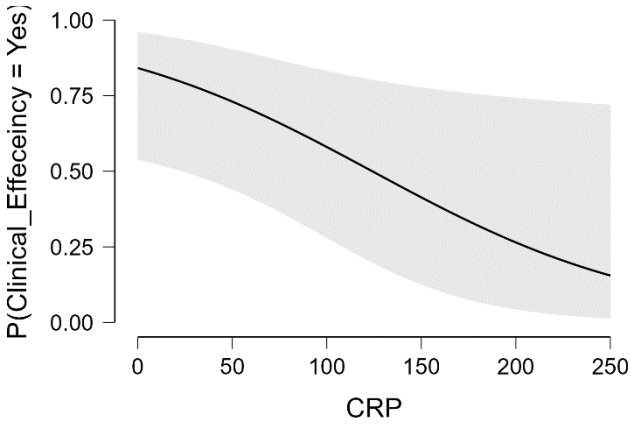
(D)


1.00
0.75
0.50
0.25
0.00
P(Clinical_Effeceincy = Yes)
No
Yes
ICU_stay

(E)


1.00
0.75
0.50
0.25
0.00
P(Clinical_Effeceincy = Yes)
No
Yes
Inotropes

(F)


1.00
0.75
0.50
0.25
0.00
P(Clinical_Effeceincy = Yes)
0
50
100
150
200
250
CRP

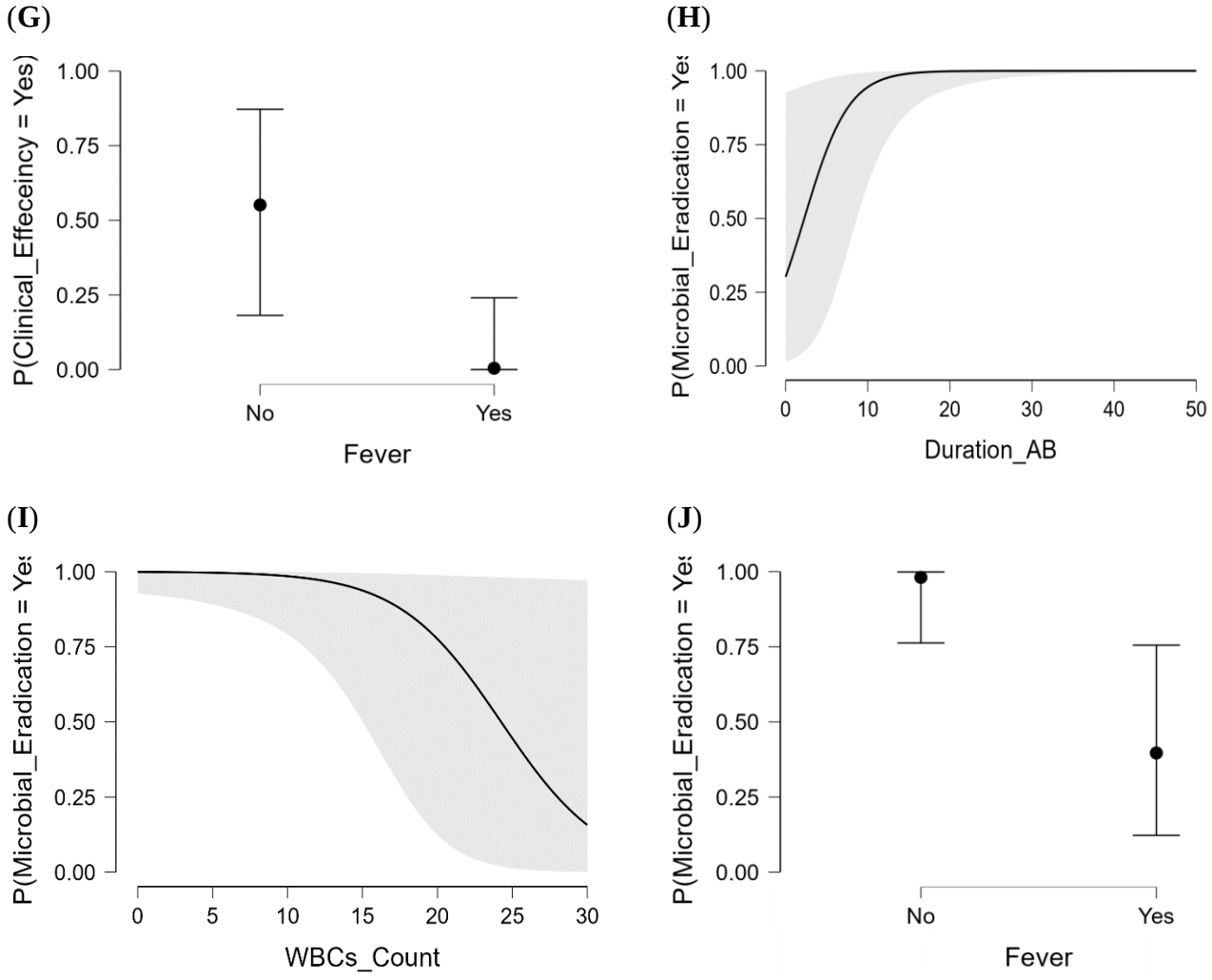


Figure 5

Conditional estimation/prediction plots for the multivariate logistic regression analyses between CAZ-AVI outcomes and independent variables (line equation) at 95% confidence intervals (shadow part). (**A**–**C**) The 30-day all-cause mortality. (**D**–**G**) Clinical efficiency. (**H**–**J**) Microbial eradication. Only parameters that were significant ($p< 0.05$) throughout the multivariate logistic regression analyses were represented.

CHAPTER V
Discussion

Due to their limited treatment options, high prevalence, and high rates of morbidity and mortality, infections with CRKP, including OXA-48-like producing enzymes, represent some of the most common carbapenem-resistant Enterobacterales and present serious public health challenges (Lu et al., 2021; Jean et al., 2022). Moreover, a greater rate of patient mortality has been associated with inadequate treatment of carbapenem-resistant illnesses (Lu et al., 2021).

The percentage of isolates with OXA-48-like pathogens grew from 0.5% to 0.9% during a three-year worldwide surveillance (2016–2018), with K. pneumonia being the most common microbe in Europe and its bordering countries (Castanheira et al., 2021). The monitoring study found that decreased susceptibility rates to meropenem and/or vaborbactam were associated with the presence of additional mutations/alterations such as OmpK35, OmpK36, and/or blaCTX-M-15 within the majority of OXA-48 isolates.

Prior to 2015, combinations of medications with high toxicity (aminoglycosides and colistin), poor pharmacokinetics (aminoglycosides, colistin, and tigecycline), and/or known microbiological resistance (carbapenem) were used as frontline treatments for carbapenem-resistant OXA-48-like CRKP (Logan and Weinstein, 2017). As the primary cause of carbapenem-resistant Enterobacterales infections in the US, K. pneumonia carbapenemases are best treated with CAZ-AVI, a new lactam/lactamase inhibitor that was approved by the FDA in 2015 (Zhen et al., 2022). Shirley and colleagues discovered that CAZ-AVI efficiently suppresses gram-negative bacteria, including isolates of drug-resistant Pseudomonas aeruginosa and extended-spectrum β-lactamase-, AmpC-, K. pneumonia carbapenemase-, and OXA-48-producing Enterobacterales (Shirley, 2018).

Data from the INFORM global monitoring program over two time periods (2012–2014) and (2015–2017) indicate that CAZ-AVI shown efficacy against the majority of carbapenem-resistant Enterobacterales isolates expressing KPC and OXA-48-like enzymes (de Jonge et al., 2016; Spiliopoulou et al., 2020). And the Infectious Diseases Society of America (Tamma et al., 2023; Tamma et al., 2020) state that CAZ-AVI is the preferred course of treatment for carbapenem-resistant Enterobacterales-producing OXA-48-like enzymes. While CAZ-AVI has shown promise against some class D (OXA-48) and Ambler class A (KPC) carbapenemases in vitro, it is ineffectual against MBL manufacturers.

The guidelines also recommend cefiderocol as a replacement since OXA-48-like enzymes that produce carbapenem-resistant Enterobacterales are resistant to both cilastatin-imipenem-relebactam and vaborbactam-meropenem. In Saudi Arabia, there are currently little clinical experiences, even though CAZ-AVI has shown promising therapeutic results in CRKP-infected patients. We assessed the microbiological and clinical efficacy of CAZ-AVI add-on therapy to the standard antibiotic regimen in this single-center cohort of OXA-48-like CRKP-infected people.

The primary findings of the study illustrated the benefits of CAZ-AVI above conventional treatment. These included reduced 30-day all-cause mortality (50.0% versus 70.0%; $p = 0.036$), lower rates of infection recurrence (7.8% versus 24.0%; $p = 0.019$), and significantly higher rates of microbial eradication (68.8% versus 42.0%; $p = 0.007$). Additionally, there were lower rates of clinical success and remission (42.2% versus 22.0%; $p = 0.028$). Furthermore, there were lower percentages of ICU hospitalizations (65.6% versus 86.0%; $p = 0.017$) and higher rates of soft tissue infections (28.1% compared 6.0%; $p = 0.003$) among the intervention patients.

The most remarkable discovery was that CAZ-AVI add-on medication showed statistically significant preferred clinical and microbiological outcomes over the control group when compared to monotherapy. Furthermore, there was a negative correlation found between patients' 30-day all-cause mortality and their gender (female gender), ICU hospitalization, and fever as independent negative predictors. Fever, CRP bio levels, and inotropes were the main risk variables affecting the clinical effectiveness of CAZ-AVI; on the other hand, ICU admission was the only component that was favorably connected with clinical effectiveness and a positive predictor.

The efficacy of CAZ-AVI to eliminate microorganisms was positively correlated with the duration of therapy; however, fever episodes and WBC levels were unfavorable, independent variables. It's interesting to note that our results agree with existing data from real-world investigations and the molecular pathways involved in getting rid of OXA-48-like CRKP strains. Research has demonstrated that CAZ-AVI is highly effective in treating carbapenem-resistant Enterobacterales infections, such as CRKP infections. This has been reported in 33.3% to 81.8% of global single-center reports and/or small-sample-sized studies (Gu et al., 2021; Martin et al., 2022; Di Pietrantonio et al., 2022; Balandín et al., 2022).

According to several studies that have been published, there is a range of 36.7% to 79.5% in CAZ-AVI-associated microbiological clearances among different kinds of carbapenem-resistant Enterobacterales infections (Mazuski et al., 2021; Wang et al., 2022; Zhang et al.,

2021). It has also been demonstrated that certain predictors, such as chest infections and an INCREMENT-CPE score of greater than seven points, have a negative effect on the 14-day clinical effectiveness of CAZ-AVI treatment for KPC-producing K. pneumonia (Castón et al., 2020).

Furthermore, our findings demonstrated that, despite a number of factors impacting these outcomes, the CAZ-AVI-treated patients had a modest level of microbiological eradication (almost 69%) and clinical success/efficiency (almost 42%). Domestic studies have demonstrated similar findings. A study by Alqahtani et al. (Alqahtani et al., 2022) found that adult CAZ-AVI treated patients who were transported to King Abdul-Aziz Medical City, Saudi Arabia between 2018 and 2020 had an overall clinical cure rate of 78%, as opposed to 42.2% in the comparable group.

According to this study, 81% of isolates carried OXA-48 enzymes, and K. pneumonia was the most common causative pathogen. The majority of patients had pneumonia that had either been contracted in the hospital or while on a ventilator. In a different study, Alraddadi et al. discovered that the OXA-48 gene was the most prevalent gene in 74% of isolates at the King Faisal Specialist Hospital and Research Center (2017–2018). Clinical cure rates with CAZ-AVI therapy were 80% (Alraddadi et al., 2019).

Although both of the latter studies demonstrated more clinical success than ours, these domestic reports did not reveal any independent variables (predictors) that could have affected their findings either clinical or microbiological success. Furthermore, our study provides thorough clinical insights for CAZ-AVI applications over larger regimens because it solely looks at the variations in clinical and microbiological outcomes across the groups under inquiry based on antibiotic regimen, monotherapy, and add-on therapy. The study by Alraddadi et al. also used a relatively limited sample size (CAZ-AVI-treated patients; n = 10), which could have a substantial impact on its findings.

Previous studies have demonstrated variable fatality rates for carbapenem-resistant Enterobacterales infections, ranging from 8.6% to up to 50% across different populations (Gu et al., 2021; Di Pietrantonio et al., 2022; Chen et al., 2021; Tumbarello et al., 2021). The study by Nagvekar et al. found that when CAZ-AVI was used either by itself or in conjunction with other medications, patients experienced a high rate of success. Additionally, the data indicated a 21% overall mortality rate, indicating that CAZ-AVI would be a suitable course of treatment for patients suffering from infections brought on by Enterobacterales that are resistant to carbapenem (Nagvekar et al., 2021).

Individuals treated with CAZ-AVI for carbapenem-resistant K. pneumonia infections showed a significantly lower 30-day mortality rate after kidney transplantation than those treated with other therapies (Zhang et al., 2021). A matched cohort whose KPC-Kpbacteremia had been treated with drugs other than CAZ-AVI had a 30-day mortality rate that was considerably higher (36.5% vs. 55.8%) than the group of 104 patients with bacteremic K. pneumonia infections that produced carbapenemase, according to Tumbarello et al. The 30-day mortality rates were found to be significantly influenced by a number of independent factors, including pneumonia, length of hospital stays, baseline creatinine clearance, the Charlson comorbidity score, an INCREMENT index of eight or higher, obesity, CAZ-AVI renal dose adjustment, prolonged CAZ-AVI infusion, and/or septic shock (Gu et al., 2021; Di Pietrantonio et al., 2022; Alqahtani et al., 2022).

In order to ascertain the effectiveness and safety of CAZ-AVI for treating carbapenem-resistant enterobacterial bloodstream infections, Chen et al. did a meta-analysis using the recovered data from 11 studies with enormous, combined patient sample sizes (n = 1205) (Chen et al., 2022). The study found that the 30-day death rate was significantly reduced in the CAZ-AVI group when compared to those on colistin-based regimens. In a trial comparing the two therapies, CAZ-AVI showed superior bacterial clearance (~43% versus 14%) and decreased 30-day mortality (~14% versus 43%) in contrast to polymyxin B (Chen et al., 2022). Our findings demonstrated lower 30-day death rates for CAZ-AVI when compared to standard therapy; unfavorable predictors included fever, ICU hospitalization, and sex (female%). These results are in line with evidence reports from earlier study.

However, in our study intervention group, there was only a 50:50 chance that CAZ-AVI would be given; as a result, 32 patients received CAZ-AVI and 32 did not. The only trial that found any discernible mortality differences between inpatients receiving CAZ-AVI and those on regimens with polymyxin or tigecycline was conducted by Alraddadi et al. (Alraddadi et al., 2019). However, the limited sample size may account for this finding. In summary, characteristics of a patient, baseline characteristics, and medication-related variables are generally associated with patient death as well as treatment regimen efficacy.

Finally, the study's retrospective methodology and the medium-sized sample's complicated co-morbidities were a drawback. Selection bias could not be totally ruled out because the study was not blind in the sense that the researcher was not aware of which treatment regimen was being used or if it was more successful when combined with CAZ-AVI. Additionally, the study lacked more thorough information on markers of liver and kidney function, indicators of the

severity of infections, and laboratory tests to assess the effectiveness of the pharamcokinetic components.

Because of the modest sample size, we were able to sub-analyze OXA-48-like variations with or without additional co-producing β-lactamase-resistant mutations. Remember that using empirical antibiotics other than OXA-48-like antibiotics before using them may affect drug efficacy and mortality. Further multicenter prospective large trials are recommended to determine the clinical effectiveness of CAZ-AVI and the suitable antibiotic regimen to supplement CAZ-AVI.

CHAPTER VI

Conclusion and Recommendations

6.1 Conclusion

When compared to typical antibiotic regimens, the present study suggests that CAZ-AVI (Ceftazidime-Avibactam) add-on therapy shows encouraging results for treating infections caused by carbapenem-resistant Klebsiella pneumoniae with bla OXA-48-like genes. When compared to standard therapies, the current study demonstrated that CAZ-AVI therapy was linked to improved clinical remission, microbiological eradication, decreased bacterial recurrence, and decreased 30-day all-cause hospital mortality.

The study investigated the effects of several variables on the clinical and microbiological results of CAZ-AVI therapy, including sex, fever, ICU hospitalizations, usage of inotropes, CRP (c-reactive protein) levels, length of CAZ-AVI therapy, and white blood cell (WBC) counts. In summary, these findings underscore the potential advantages of CAZ-AVI therapy for complicated infections, but they also point to the necessity of additional studies to improve treatment approaches.

6.2 Recommendations

It is advised that the dosage of CAZ-AVI be tailored to the specific risk factors of each patient in order to maximize effectiveness. This means administering the drug while keeping the patient's particular circumstances and characteristics in mind. This study supports prospective multicenter investigations and randomized controlled trials.

Regarding monitoring, regular evaluation of CAZ-AVI blood level and appropriate medication adjustment. Future studies should focus on the precise dosage of CAZ-AVI based on patient-specific characteristics such liver and renal function, infection locations, and bacterial resistance mechanisms.

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Appendices

Appendix 1: Data collection sheet

CONTROL GROUP ☐ INVESTAGATION GROU☐
PATIENT NAME: ----------☐----------
MEDICAL No.: ---------- AGE: ---------- sex: MALE FEMALE ☐
CO-MORBID DISEASE: ----------☐---------

HARBORING GENE: ----------SITE OF INFECTION: ----------Date: --------
ANTIBIOTIC REGIMEN: ----------
DURATION OF REGEMIN: ----------
ICU STAY ☐ NON-ICU STAY ☐

CLINICAL REMISSION AFTER EOT: CBC: NORMA☐ ------ ABNORMAL ----------
CRP NORMAL ☐ --------ABNORMA☐ ---------NA☐
PCT NORMAL ☐ ----- ABNORMAL ☐ --------- NA ☐
FEVER YES ------ NO ----------
REMISSION YES☐ NO ☐
ALL CAUSE MORTALITY WITHEN 30 DAYS ☐ ☐
DIED ☐ SURVIV☐
RECURRENT SAME PATTERN OF BACTERIA AFTER 90 DAYS OF STARTING OF AB REGEMIN
YES ☐ NO ☐
MICROBIAL ERADICATION AFTER EOT (CULTURE NEGATIVE)
YES, NO ☐ ☐ DATE: ----------
DURATION BY DAYS OF THERAPY (WHEN REACH NEGATIVE CULTURE): ----------
---
Use of Inotropes ----------

Date			
WBC			
Neutrophile			
CRP			

Antibiotic Regimen:	starting date	finishing date
----------	----------	----------
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Appendix

Appendix 2:

ARMED FORCES HOSPITALS
SOUTHERN REGION

ACADEMIC AFFAIRS الشـــؤون الأكاديمية

Research Ethics Committee

To: Principal Investigator/Researcher
Dr. Ali Hawan, Microbiology Consultant

Co-Investigators:
Dr. Ali Shehri
Mr. Sultan Al-Kahtani
Dr. Ali Maamon Abu Jaber

Date: December 4, 2022

Subject: **IMPACT OF ADDING CEFTAZIDIME/AVIBACTAM TO STANDARD THERAPY IN TREATED PATIENT INFECTED WITH CRE KLEBSIELLA PNEUMONIA OXA 48 LIKE BACTERIA**
Code:AFHSRMREC/2022/MICROBIOLOGY /661

The Committee has received the above-mentioned research proposal and carefully reviewed it and it was approved.

Please do not hesitate to ask for any assistance at any time should you need it.

Thank you very much!

Dr. Rafaat Morched Chakik
Chairman, Research Ethics Committee

ARMED FORCES HOSPITALS SOUTHERN REGION
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Appendix

Appendix 3: Curriculum vitae for Author

Personal information:

NAME,SURNAME:	Al MaamonR.Tawfiq Abu Jaber
DATEofBIRTHand PLACE:	11/4/1980, Kuwait

CURRENTOCCUPATION:Ph.D.student,Senior clinical pharmacist, AFHSR, KSA.

ADDRESSofCORRESPONDENCE:ShafaBadran, Amman, Jordan

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Education:

YEAR	GRADE	UNIVERSITY	FIELD
1998-2003	Bachelordeg.	Jordan University	Pharmacy
2005-2007	Master deg.	Jordan University	Clinical pharmacy
2019-2024	Ph.D.	NearEastUniversity	Clinical pharmacy

Professional experiences:

PERIOD	TITLE	INSTITUTION	COUNTRY
2022- PRESENT	Senior clinical pharmacist	Armed Forces Hospital	KSA
2021-2022	Pharmacy Manager	Arab Medical center	Jordan
2013-2019	Head of clinical pharmacists	Armed forces Hospital	KSA
2012-2013	Clinical Lecturer	King Faisal University	KSA
2009-2012	Clinical pharmacist	Armed Forces Hospital	KSA
2008-2009	Senior pharmacist	Dr SulaimanAlhabib Hospital	KSA
2004-2008	Staff Pharmacist	Islamic Hospital	Jordan