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ANTIBACTERIAL DRUG EXPOSURE AND RISK OF CARBAPENEM-RESISTANT KLEBSIELLA PNEUMONIA: A REVIEW

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Abstract

This review examines the growing threat of Carbapenem-resistant *99 (CRKP), focusing on the role of antibacterial drug exposure in the emergence and spread of resistance. The review explores the mechanisms of carbapenem resistance, including the production of carbapenemases (e.g., KPC, NDM, OXA-48), as well as non-carbapenemase mechanisms like porin alterations and efflux pump overexpression. Key findings highlight the significant contribution of the overuse and misuse of antibiotics, particularly carbapenems, broad-spectrum cephalosporins, and fluoroquinolones, in promoting resistance. It emphasizes the importance of optimizing antibiotic use through antimicrobial stewardship, implementing stringent infection control measures, and developing novel therapeutic strategies. Understanding how antibacterial drug exposure influences CRKP resistance is crucial for informing better treatment practices and global efforts to combat antimicrobial resistance.*

INTRODUCTION

K. pneumoniae is a member of the Enterobacteriaceae family and is a Gram-negative, facultative anaerobic bacterium. (Janda et al., 2021) Common opportunistic pathogen especially in immune-compromised individuals, it is responsible for a wide range of healthcare-associated infections (HAIs). *K. pneumoniae*-related infections include intra-abdominal infections, urinary tract infections, bloodstream infections, and pneumonia. (Sahadulla et al., 2019). Especially in critical care units (ICUs) and among patients with underlying illnesses including diabetes, cancer, or chronic kidney disease, it is a common cause of nosocomial infections. (Trubiano et al., 2015). The bacterium's capacity to build biofilms on medical devices, as well as its survivability in hospital surroundings, make it highly contagious, causing epidemics in healthcare settings. (Percival et al., 2015). *K. pneumoniae* is a key contributor to morbidity and death in hospitalized

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patients, so it poses a notable strain on healthcare systems all around. (Effah et al., 2020).

Emergence of Carbapenem-Resistant Strains and the Challenges They Pose to Treatment

The treatment of infections brought on by this disease has been significantly impacted by the rise of carbapenem-resistant *K. pneumoniae* (CRKP). Carbapenems, a type of β-lactam antibiotic, have historically been regarded the last line of defence against multidrug-resistant Gram-negative bacteria like *K. pneumoniae*. (Karampatakis et al., 2023). However, the emergence of carbapenem resistance has significantly reduced therapeutic options. (Fritzenwanker et al., 2018). In *K. pneumoniae*, carbapenem resistance is predominantly induced by the production of carbapenemases, enzymes that degrade the β-lactam ring of carbapenems, thereby rendering them ineffective. (Aurilio et al., 2022). *K. pneumoniae*'s carbapenemases include KPC, NDM, and OXA-48. (Sharma et al., 2016) These resistant strains are extremely infectious and frequently resistant to other antibiotic classes, such as cephalosporins and fluoroquinolones, complicating treatment options. CRKP's proliferation poses substantial obstacles to infection control and clinical management, as these strains have the potential to result in treatment failures, protracted hospital stays, and elevated mortality rates. (Karampatakis et al., 2023).

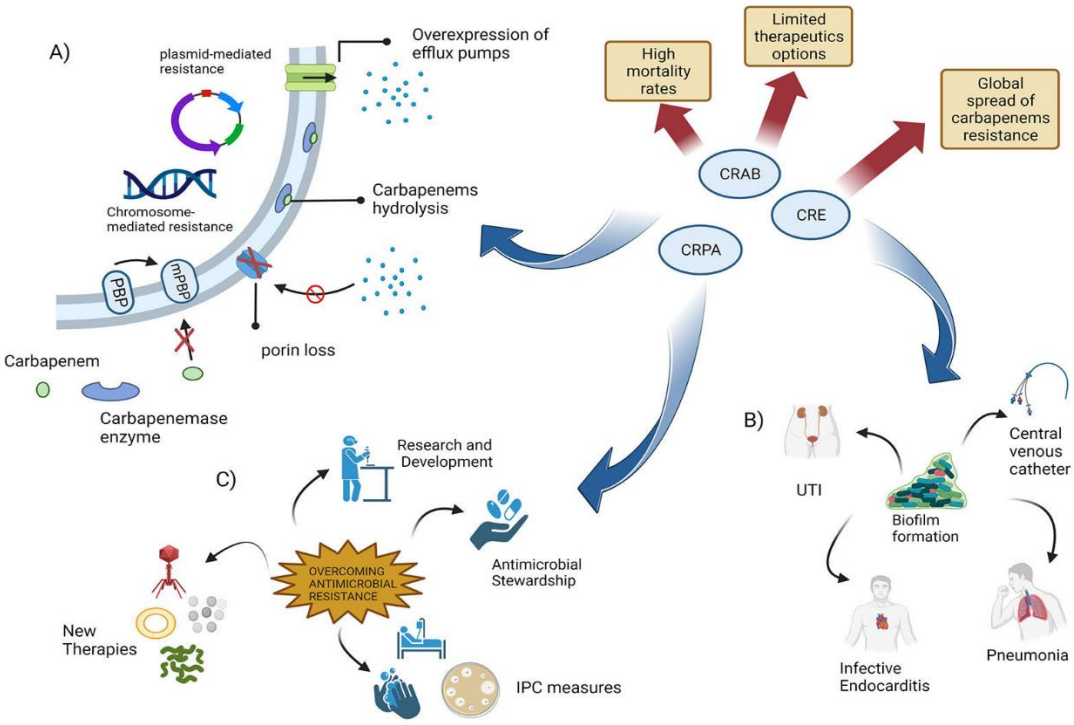

Figure 1: Mechanisms of Carbapenem Resistance and Strategies for Combatting *K. pneumoniae* Infections

Figure 1 shows the intricate processes by which *K. pneumoniae* develops resistance to carbapenems as well as ways to reduce this resistance. Panel A emphasises the mechanisms of resistance, including plasmid-mediated and chromosome-mediated resistance, overexpression of efflux pumps, carbapenem hydrolysis by carbapenemase enzymes, and loss of porins. These systems help to limit antibiotic entrance and promote antibiotic ejection from bacterial cells. Panel B displays the clinical consequences of carbapenem resistance, such as urinary tract infections (UTIs), pneumonia, and infective endocarditis, which are aggravated by biofilm formation and central venous catheter implantation. Panel C depicts antimicrobial resistance-overcoming strategies, such as research and development of novel medicines, antimicrobial stewardship programs, and infection control measures (IPC) to limit the spread of resistant strains. Figure 1 highlights the global expansion of

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resistance and the critical need for effective therapeutic choices and preventative measures. (Mancuso et al., 2023).

The Role of Antibacterial Drug Exposure in the Development of CRKP

Antibacterial drug exposure is a critical factor in the development and dissemination of carbapenem-resistant *K. pneumoniae* (CRKP). (Li et al. 2020) Antibiotic abuse and misuse, particularly in hospital settings, generate selective pressure that promotes the survival of resistant strains. (Cantón et al., 2013) Carbapenem-resistant bacteria are much more likely to be selected for when broad-spectrum antibiotics, particularly carbapenems, are used excessively or inappropriately, according to studies. (Wilson et al., 2017) This occurs as a result of the killing of susceptible bacteria by antibiotics, which in turn enable resistant strains to survive and dominate. Additionally, resistant bacteria may be selected as a result of prolonged antibiotic therapy and improper dosing (Mancuso et al., 2021). In addition to carbapenems, usage of third-generation cephalosporins and fluoroquinolones raises the likelihood of CRKP infections, as these medicines can cause cross-resistance in *K. pneumoniae*. (Gümüş et al., 2023) Antibiotic stewardship, or the right use of antibiotics, is thus crucial in preventing the growth of CRKP and other multidrug-resistant organisms. (Okieah et al., 2021)

The primary goal of this review is to investigate the effect of antibiotic use on the development and dissemination of carbapenem-resistant *K. pneumoniae* (CRKP). Given the growing threat of CRKP and its resistance to last-line antibiotics, it is critical to understand how diverse patterns of antibiotic exposure contribute to the evolution of resistance. In order to investigate the relationship between the elevated risk of CRKP infections and the overuse and misuse of antibiotics, particularly carbapenems and other broad-spectrum agents. The review offers insights on the mechanisms by which antibacterial medications encourage resistance, the need of antimicrobial stewardship, and recommendations for reducing CRKP dissemination. The clinical practices and infection control strategies with the necessary information to mitigate the proliferation of CRKP along with other multidrug-resistant infections in healthcare contexts.

Classification of CRKP:

Resistant to carbapenem for *K. pneumoniae* (CRKP), this means strains of *K. pneumoniae* that are no longer killed by carbapenems. These are drugs that are usually only used as a last option against MDR bacteria (Shen et al., 2020). A variety of illnesses linked to healthcare, such as pneumonia, bloodstream infections, urinary tract infections and intra-abdominal infections, are frequently caused by the Gram-negative bacterium *K. pneumoniae* (Pang et al., 2019). Treating *K. pneumoniae* becomes especially difficult when it develops resistance to carbapenems since these drugs are usually used to control serious infections brought on by MDR organisms (Tumbarello et al., 2018). CRKP strains are often classified according to the carbapenemase enzymes it generate, which are responsible for carbapenem breakdown (Papp-Wallace et al., 2017). New Delhi's metallo-β-lactamase (NDM), the *K. pneumoniae* carbapenemase (KPC), and OXA-48 are the primary carbapenemases identified in *K. pneumoniae* (Fournier et al., 2018). The advent of these drug-resistant strains poses a substantial therapeutic issue due to the scarcity of treatment alternatives (Leavitt et al., 2021).

Global Prevalence and the Public Health Threat Posed by CRKP

CRKP has become a serious public health problem in recent years due to its rapidly increasing global frequency (Guzmán et al., 2020). Initially, carbapenem resistance was most widely documented in North America and Europe, but the problem has since spread globally, with significant rates of CRKP discovered in hospitals in Asia, Africa, and Latin America (Cai et al., 2020). According to research, the emergence of CRKP is especially concerning in nations with a significant number of hospital-acquired infections, in which broad- spectrum antibiotics, including carbapenems, are frequently used and uncontrolled (Mavrogiorgos et al., 2019). CRKP infections have been linked to increased morbidity and mortality in healthcare settings, particularly intensive care units (ICUs) (Zong et al., 2020). International travel, healthcare worker

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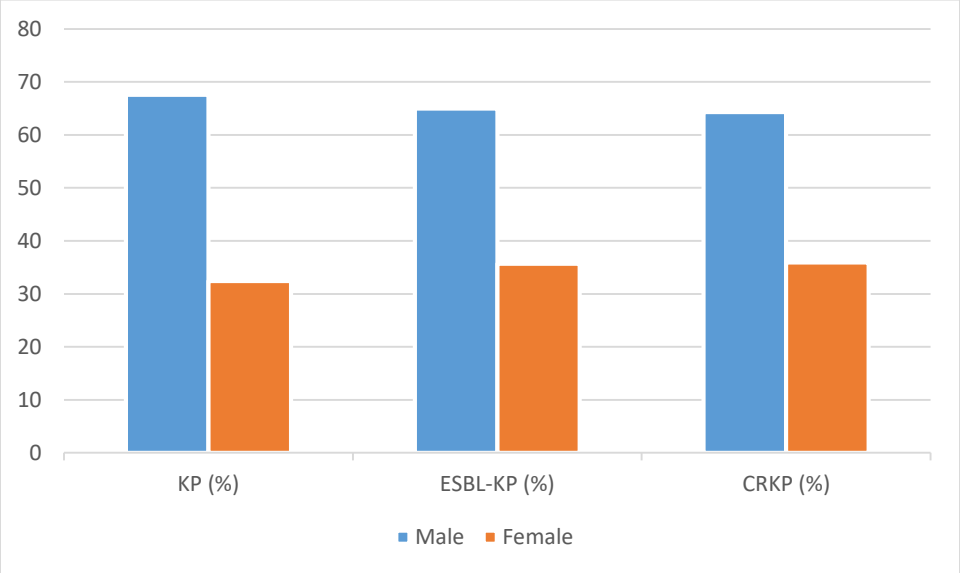
movement, and widespread antibiotic usage in both human and veterinary medicine have all contributed to the global proliferation of CRKP strains (Suarato et al., 2020). CRKP poses a concern not only to individual patients, but also to healthcare systems due to increasing treatment complexity and higher expenses associated with controlling infections that are resistant (Zhang et al., 2021).



Graph 1: Gender Distribution of *K. pneumoniae* (KP), Extended-Spectrum Beta-Lactamase-Producing *K. pneumoniae* (ESBL-KP), and Carbapenem-resistant *K. pneumoniae* (CRKP) Infections

In the first graph, we can see a comparison between the percentage of male and female infections caused by *K. pneumoniae* (KP), ESBL-KP, and CRKP as all of them. The statistics suggest that males have a higher proportion of KP infections (about 67%) than females (32%). Similarly, ESBL-KP infections affect a higher percentage of males (about 65%) than females (35%). The proportion of CRKP infections is slightly more balanced, however males still have a larger rate (about 64%) than females (36%). These findings imply that males have a little higher prevalence of KP, ESBL-KP, and CRKP infections than females, which might help guide healthcare policies and interventions for these populations.

Table 1: Proportion of KP, ESBL-KP, and CRKP Infections by Age Group (Panel B)

Age Group	KP (%)	ESBL-KP (%)	CRKP (%)
<1	5.4	16.2	10.4
1-10	2.6	1.4	2.6
11-20	3.5	2.6	0.3
21-30	1.4	2.6	0.5
31-40	2.6	0.5	3.1
41-50	3.5	2.6	0.5
51-60	8.5	17.1	13.8
61-70	7.2	6.5	6.5

The Mechanisms behind Carbapenem Resistance in *K. pneumoniae*

The primary mechanism by which carbapenem resistance in *K. pneumoniae* is mediated is the production of carbapenemase enzymes, which degrade carbapenems and make them ineffective (Bialek-Davenet et al., 2020). A *K. pneumoniae* carbapenemase (KPC), an NDM, and an OXA-48 are

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the three main types of carbapenemases that can be found in this bacteria (Woodford et al., 2019). KPC, a serine β-lactamase, is the most pervasive carbapenemase in the United States and has become a significant contributor to CRKP infections worldwide (Paterson et al., 2018). NDM is a metallo-β-lactamase that makes bacteria resistant to almost all β-lactam antibiotics, even carbapenems. It has been found a lot in South Asia and some places in Europe (Kumarasamy et al., 2019). Another serine β-lactamase, OXA-48, is being found more often in *K. pneumoniae* isolates from the Mediterranean area and sections of Asia (Livermore et al., 2020). These carbapenemases can be expressed on plasmids, which are movable genetic components that allow for the horizontal transmission of resistant genes between bacteria (Sennati et al., 2020). In both hospital and community contexts, the rapid spread of CRKP strains is a significant concern due to their capacity to transfer genetic material (Braga et al., 2019). *K. pneumoniae* bacteria can become more resistant to carbapenems by changing porin channels (which make it harder for antibiotics to get in), making too many efflux pumps, and changing penicillin-binding proteins (PBPs), all of which help the bacteria stay alive even when antibiotics are present (Anand et al., 2021).

The Clinical Impact of CRKP Infections in Terms of Morbidity, Mortality, and Healthcare Costs

The clinical consequences of CRKP infections are significant, as they contribute to elevated healthcare costs, morbidity, and mortality (Bassetti et al., 2020). Because there are few treatment options for CRKP infections, patients may require extended hospital admissions, increasing the risk of consequences, include the transmission of the infection among other patients (Zong et al., 2020). Severe sepsis, septic shock, and organ failure are potential outcomes of the most prevalent CRKP-associated infections, including pneumonia and bloodstream infections (Papp-Wallace et al., 2019). Such complications contribute to elevated mortality rates. Research has indicated that CRKP infections are linked to greater death rates than those caused by carbapenem-susceptible *K. pneumoniae* strains (Tumbarello et al., 2018). For instance, according to Braga et al. (2019), patients with CRKP infections, especially those with impaired immune systems or other medical disorders, had a substantially increased risk of death (Tumbarello et al., 2018). CRKP infections also have a significant economic impact since their care usually calls for long-lasting antibiotic therapy, different, more costly medications, and protracted hospital stays (Karanika et al., 2020). Furthermore, the growth of CRKP in healthcare settings needs additional infection control measures, such as isolation protocols and improved cleaning techniques, which drive up healthcare expenses (Tee et al., 2020). The rising number of cases of CRKP shows how important it is to quickly improve infection control, create new drug stewardship programs, and come up with new ways to treat these pathogens that are resistant (Jiang et al., 2021).

Mechanisms of Carbapenem Resistance in Klebsiella pneumoniae

K. pneumoniae carbapenem resistance is a multifaceted phenomenon that is predominantly driven by the production of carbapenemases. However, other resistance mechanisms, such as the overproduction of beta-lactamases and changes in porin channels, are additionally contributing to the resistance phenotype. A comprehensive analysis of the processes underlying carbapenem resistance in *K. pneumoniae* is provided below.

Types of Carbapenemases and Their Mechanisms

Carbapenem resistance in *K. pneumoniae* is frequently linked to the generation of carbapenemases, enzymes that hydrolyse carbapenem antibiotics, leaving them ineffective (Chavada et al., 2020). *K. pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), and OXA-48 are the three main types of these carbapenemases based on their molecular structure and how they work (Livermore et al., 2020). Every one of these enzymes increases resistance by means of several mechanisms:

1. ***K. pneumoniae* Carbapenemase (KPC)**

Cephalosporins, carbapenems and other β-lactams become ineffective by KPC, a serine-based β-lactamase. KPC is the carbapenemase that is most common in *K. pneumoniae* strains around the world, especially in the US and some regions in Europe (Bialek-Davenet et al., 2020).

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2. **New Delhi Metallo-β-lactamase (NDM)**

According to Kumarasamy et al. (2020), NDM is a zinc-dependent metallo-β-lactamase that confers resistance to several β-lactam antibiotics, including carbapenems. Strains of *K. pneumoniae* that produce NDM have proliferated worldwide, with a particular focus on South Asia. Plasmids containing NDM enable its horizontal transfer between different bacterial species.

3. **OXA-48**

OXA-48 is a class D β-lactamase that hydrolyses the β-lactam ring using a different mechanism than KPC and NDM. It is showing up in more and more *K. pneumoniae* isolates in Asia, the Mediterranean, and Europe, although it isn't as effective as KPC at hydrolyzing carbapenems. Strains of *K. pneumoniae* that are circulating in the Middle East and Europe often have OXA-48. (Zong et al., 2020).

Table 2: Carbapenemase Types, Mechanisms, Prevalence, and Locations of Emergence in Klebsiella pneumoniae

Carbapenemase	Mechanism	Prevalence	Location of Emergence
KPC	Serine-based β-lactamase, hydrolyzes carbapenems	Common in US and worldwide	Hospitals, healthcare settings
NDM	Metallo-β-lactamase requiring zinc, broad-spectrum	Common in South Asia	Emerging globally
OXA-48	Class D β-lactamase, hydrolyzes carbapenems	Increasing in Europe & Asia	Mediterranean, hospital outbreaks

Non-Carbapenemase Resistance Mechanisms

The overproduction of beta-lactamases, modifications in porin channels, and efflux pump activity are some of the non-carbapenemase methods by which *K. pneumoniae* may demonstrate resistance. (Khalifa et al., 2021).

1. **Changes in Porin Channels**

Porins are proteins found on bacterial cell membranes that facilitate the uptake of antibiotics. *K. pneumoniae* can change their shape or lower the quantity of porins, therefore blocking carbapenems from getting into the bacterial cell. A major cause of carbapenem resistance is this lower drug permeability. (Gogoi et al., 2023).

2. **Efflux Pumps**

K. pneumoniae has the ability to express efflux pumps, which are capable of actively expelling antibiotics from the bacterial cell, thereby decreasing the intracellular concentration of the drug. Overexpression of these pumps may contribute to *K. pneumoniae* resistance to carbapenems as well as other antibiotics such as fluoroquinolones and cephalosporins. (Padilla et al., 2010).

3. **Beta-Lactamase Overproduction**

Overproduction of ESBLs or other β-lactamases can increase resistance to carbapenems. These enzymes break down β-lactam antibiotics, including third-generation cephalosporins, and can enhance resistance when paired with carbapenemase synthesis. (Sheikh et al., 2015)

Table 3: Non-Carbapenemase Mechanisms of Resistance in *K. pneumoniae* and Their Impact on Carbapenem Resistance

Non-Carbapenemase Mechanism	Mechanism of Resistance	Impact on Carbapenem Resistance
Porin Channel Alteration	Reduction or mutation of porins limiting antibiotic entry	Reduces permeability to carbapenems
Efflux Pumps	Active expulsion of antibiotics from bacterial cells	Lowers intracellular carbapenem concentration
Beta-Lactamase Overproduction	Increased production of β-lactamases (e.g., ESBLs) that degrade β-lactams	Increases breakdown of carbapenems and other β-lactams

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Role of Horizontal Gene Transfer in the Spread of Resistance

Keyhole limpet (*K. pneumoniae*) resistance genes, particularly carbapenemase producing genes, are acquired through horizontal gene transfer (HGT). (Han et al., 2025) Because of this transfer, resistant strains can quickly spread their resistance traits through bacterial populations. This makes it possible for carbapenem-resistant pathogens to spread in hospital settings and the wider community. (Li et al., 2022) Bacteria exchange genetic material, including plasmids, transposons, or integrons, through the most prevalent mechanisms of HGT: transformation, conjugation, and transduction.

Carbapenem resistance spreads in *K. pneumoniae* via a variety of horizontal transfer of genes pathways. Transformation, in which *K. pneumoniae* absorbs free DNA from the environment including carbapenemase genes from other bacteria, is one of the main mechanisms (Godeux et al., 2022). Another important technique is conjugation, which transfers plasmids—often containing several antibiotic resistance genes—from one bacterium to another. The most prevalent mechanism of resistance gene dissemination in *K. pneumoniae* is this (Navon-Venezia et al., 2017). Finally, carbapenem resistance is characterised by transduction, which involves the transmission of resistance genes by bacteriophages (Schneider et al., 2021). These processes contribute to the increasing danger of infections caused by carbapenem-resistant *K. pneumoniae* by allowing resistance to spread quickly among bacterial populations.

Plasmids, which often carry carbapenemase genes like KPC and NDM, are of particular concern because they are mobile genetic elements that can be transferred between bacteria, contributing to the rapid spread of carbapenem resistance across different species.

Contribution of Mobile Genetic Elements (Plasmids, Transposons) to Resistance Gene Acquisition

The acquisition and spread of resistance genes in *K. pneumoniae* is significantly influenced by mobile genetic components including plasmids, transposons, and integrons (Partridge et al., 2018). The replication of plasmids is independent of chromosomal DNA and they frequently contain resistance genes. They are small, circular DNA molecules. Conjugation can transmit these plasmids between bacteria, allowing resistance to proliferate horizontally (Dimitriu et al., 2022).

Plasmids: Plasmids containing carbapenemase genes—such as KPC, NDM—can be moved between bacteria of the same or different species, therefore enabling the spread of carbapenem resistance throughout several bacterial populations. (Kopotsa et al., 2019).

Transposons: Plasmids containing carbapenemase genes—such as KPC, NDM—can be moved between bacteria of the same or different species, therefore enabling the spread of carbapenem resistance throughout several bacterial populations. (Kopotsa et al., 2019).

Integrons: There are genetic factors called integrons that can grab and add gene cassettes, which usually have antibiotic resistance genes, to the chromosomes of bacteria or plasmids. (Hall et al., 2007)

When these mobile genetic components come together, they make *K. pneumoniae* more adaptable and more likely to survive in healthcare settings like hospitals, where antibiotics are used often, which speeds up the spread of resistance.

Role of Antibacterial Drug Exposure in the Development of CRKP

Prolonged exposure to antibiotics is one of the main reasons why resistant bacterial types like carbapenem-resistant *K. pneumoniae* (CRKP) appear and spread (Peirano et al., 2020). Antibiotics, particularly broad-spectrum agents, induce selective pressure on bacterial populations, which enables resistant strains to persist and increase in number (Tumbarello et al., 2019). Antibiotics eradicate susceptible bacteria, resulting in the development of resistant strains that can persist in the presence of the antibiotic (Chen et al., 2021). This process speeds up the growth of bacteria that are resistant to antibiotics, especially in places like hospitals and intensive care units (ICUs) where antibiotics are used a lot (Balkhair et al., 2020). With CRKP, excessive antibiotic use—particularly carbapenems—has been linked as a major

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cause of resistance growth (Hajialilo et al., 2021). To stop the spreading of CRKP, it is important to know how drug use affects resistance.

Prolonged and Unnecessary use of Carbapenems

Many people think that carbapenems are the last line of defence against bacteria that are multidrug-resistant (MDR), like *K. pneumoniae* (Tumbarello et al., 2020). However, one of the most prominent causes contributing to the increase of CRKP is the excessive and unnecessary use of carbapenems (Gandhi et al., 2021). Research has indicated that patients in intensive care units or those receiving invasive treatments who have prolonged courses of carbapenem medication are at much increased risk for getting CRKP infections (Alkundi et al., 2020). Resistance is substantially elevated by the inappropriate utilisation of carbapenems, such as their prescription for infections induced by non-resistant pathogens or for conditions that do not necessitate carbapenem treatment (Chakraborty et al., 2021). Overuse of carbapenems creates selective pressure on bacterial populations, therefore promoting the survival of *K. pneumoniae* strains with acquired resistance mechanisms including carbapenemase production (Bassetti et al., 2021). As a result, carbapenem-resistant bacteria proliferate and future patients will have less success with these medications (De Oliveira et al., 2020).

Broad-Spectrum Antibiotics and Their Contribution

Apart from carbapenems, additional broad-spectrum antibiotics such fluoroquinolones and third-generation cephalosporins are also essential for the development of CRKP (Pang et al., 2020). According to Fournier et al. (2019), third-generation cephalosporins, which are frequently recommended for a range of illnesses brought on by Gram-negative bacteria, have been linked to an increased risk of contracting CRKP infections. Certain medicines, such as ceftriaxone and cefotaxime, target a variety of bacteria, including *K. pneumoniae*, and hence apply selective pressure on bacterial populations (Mavrogiorgos et al., 2020). It has been demonstrated that extended exposure to cephalosporins raises the possibility of selecting for CRKP strains because these bacteria can develop resistance by producing extended-spectrum beta-lactamases (ESBLs), which give them resistance to beta-lactam antibiotics that are widely used, including cephalosporins (Zhang et al., 2020).

Likewise, another category of broad-spectrum antibiotics often used to treat a great variety of diseases is fluoroquinolones, including ciprofloxacin and levofloxacin (Gonzalez et al., 2021).

Fluoroquinolones, on the other hand, have been shown to help CRKP form by changing how bacteria copy DNA and divide (Sharma et al., 2020).

Fluoroquinolone-resistant genotypes of *K. pneumoniae* frequently possess additional resistance mechanisms, such as carbapenemase production, which increases their likelihood of acquiring complete resistance to carbapenems (Alfred et al., 2021). According to Alfarisi et al. (2021), CRKP strains are commonly selected due to the excessive or improper usage of broad-spectrum agents.

Antibiotic Prescribing Practices in Healthcare

The development of CRKP is significantly influenced by the inappropriate prescribing of antibiotics in healthcare settings. Several reasons contribute to the misuse of antibiotics, notably in hospitals. When doctors don't know what kind of bacteria a patient has, they may give them broad-spectrum antibiotics on after they wait for culture results. This can put critically sick patients at risk of treatment delays (Peirano et al., 2021). Furthermore, even when antibiotics are not required, patients or family members frequently put pressure on doctors to prescribe them (Jiang et al., 2020). Without considering the possibility of resistance development, doctors may choose to prescribe broad-spectrum antibiotics as a precaution or for convenience (Al-Hassan et al., 2020).

Another important reason that leads to the improper use of antibiotics is the absence of reliable testing equipment that can quickly detect particular infections. Broad-spectrum antibiotics, such as carbapenems, are overprescribed in many healthcare settings due to the inability to promptly identify the causative agent of an infection (Sennati et al., 2021). Additionally, antimicrobial stewardship may be deficient in certain healthcare settings, particularly those with significant patient turnover or insufficient resources, which could result in uneven antibiotics

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prescribing practices (Hajialilo et al., 2021). These elements work together to cause antibiotic misuse, which promotes the emergence of CRKP and other resistant diseases. Addressing these problems and making sure that antibiotics are used properly in healthcare settings require effective antimicrobial stewardship programs (Chen et al., 2020).

The goal of antibiotic stewardship is to reduce the likelihood of antibiotic resistance while simultaneously increasing the efficiency of antibiotic treatment. It is impossible to overestimate the significance of antimicrobial stewardship in reducing the risk of CRKP. Making sure that antibiotics are only provided when necessary, at the right dosage, and for the right amount of time is the main goal of antimicrobial stewardship programs (Bassetti et al., 2021). These initiatives aim to decrease the selection pressure that leads to the evolution of resistance strains, such as CRKP, by promoting careful consumption of antibiotics. This reduces the amount of bacteria that are exposed to antibiotics without necessity (Liu et al., 2021).

Research has indicated that hospital use of antibiotic stewardship initiatives can greatly lower the frequency of CRKP infections. Usually, these initiatives demand for constant tracking of antibiotic usage, clinician feedback on their prescribing patterns, and encouragement of recommendations for suitable use of antibiotics (Koh et al., 2020). Stewardship programs also usually incorporate infection control actions like hand cleanliness and isolation policies to help stop the spread of resistant pathogens. In the end, maintaining the efficacy of current antibiotics, avoiding the spread of novel resistance strains, and lowering the public health load connected with CRKP and other multidrug-resistant pathogens depend on good antibiotic stewardship (Leavitt et al., 2021).

Risk Factors for Acquiring CRKP Infections

1. Hospital and ICU Environments

Hospitals are important sites for the spread of carbapenem-resistant *K. pneumoniae* (CRKP), especially intensive care units (ICUs). There are various aspects of hospital environments that contribute to the occurrence of CRKP in healthcare settings. At the top of the list is the fact that hospital-acquired illnesses are more common among patients with extended hospital stays, particularly those in intensive care units. Extended stays provide abundant possibilities for resistant bacteria such as CRKP to colonies and propagate in the healthcare setting (Sundararajan et al., 2020). Moreover, ICUs are often filled with patients who are critically sick, have compromised immune systems, and need rigorous care and monitoring, all of which foster an environment favorable to the spread of resistant bacteria (Weiner-Lastinger et al., 2020).

A number of factors contribute to the transmission of CRKP in healthcare settings, including the frequent use of antibiotics, intrusive procedures, and close patient contact. Overuse of carbapenems and other broad-spectrum antibiotics can promote the spread and selection of CRKP strains (Almasoud et al., 2021). Hospitals with bad infection control policies could also experience CRKP outbreaks from inadequate sterilization, poor hand hygiene, and ineffectual isolation techniques. The movement of patients between wards and high ICU patient turnover also helps to spread resistant strains inside hospitals (Gonçalves et al., 2021).

2. Patients with Weakened Immune Systems

Immune-compromised patients, such as those on immunosuppressive medication, undergoing organ transplantation, or enduring chemotherapy, are more likely to get CRKP infections. Defending the body against bacterial infections depends on the immune system; when it is affected, like in immune-compromised individuals, the body gets more vulnerable to opportunistic pathogens such *K. pneumoniae* (Sujatha et al., 2021). Because of this, people with weakened immune systems are more susceptible to infections brought on by bacteria that are resistant to carbapenem. For example, chemotherapy patients are especially vulnerable to infections since chemotherapy medications not only attack cancer cells but also impair bone marrow function, hence lowering the generation of white blood cells necessary for combating infections (Ali et al., 2020). Transplant patients taking immunosuppressive medications to avoid organ rejection have likewise reduced immune responses, which increases their vulnerability to hospital-acquired infections like CRKP. The growing use of antibiotics to control infections in these patients also

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increases the risk of CRKP infections since it promotes the selection of resistant strains (Jin et al., 2020).

3. Invasive Procedures and Medical Devices

Invasive treatments and medical devices including central lines, ventilators, and catheters greatly raise the chance of contracting CRKP infections. In order to colonies internal organs, microorganisms can enter the body directly through these devices (Sakoulas et al., 2020). Infections of the urinary tract and the bloodstream are frequent complications of catheters, especially urinary and central venous catheters, respectively. Infections can develop when bacteria build up a biofilm on these devices by using them for an extended period of time (Maki et al., 2020).

Another important element in the acquisition of CRKP is ventilators, particularly in severely ill patients who need mechanical ventilation for long durations. Common problems for these patients are ventilator-associated pneumonia (VAP), which ventilators exacerbate by promoting bacterial colonization in the respiratory tract (Papadimitriou-Olivgeris et al., 2020). Bacteria, such as CRKP, which are resistant to carbapenems, can grow in biofilms on the surface of ventilator tubing and spread to patients' lungs. The risk of bacterial infection and the spread of resistant strains in hospital settings is increased by the frequent and extended use of invasive equipment (Sharma et al., 2021).

Patients are more susceptible to CRKP infections if they have underlying chronic illnesses including diabetes, heart disease, or chronic renal disease. A compromised immune system, impaired blood flow, and other physiological alterations that compromise the body's ability to defend against infections are common outcomes of chronic diseases (Arias et al., 2020). As an example, diabetes mellitus makes people more susceptible to infections and alters the function of white blood cells, both of which weaken the immune response. More so, infections, such as CRKP, are more common in diabetic patients because their high blood sugar levels foster bacterial development (Sotgiu et al., 2021).

Another important factor that increases the likelihood of CRKP infections is chronic renal failure. Antibiotic resistance can develop when patients with renal failure, especially those on haemodialysis, are exposed to the same drugs over and over again (Lee et al., 2020). Another factor that raises the risk of CRKP infections is the requirement for dialysis, which involves frequent bloodstream access. Chronic diseases can result in regular hospital stays and extended medical treatments, which raise the risk of exposure to healthcare-related infections such as CRKP (López et al., 2020).

In general, the immune system's ability to fend off infections that have developed resistance is compromised when underlying chronic diseases are present. Patients with chronic illnesses are more sensitive to developing CRKP infections when paired with extended hospital stays and antibiotic exposure (Anwar et al., 2021).

Global Spread and Epidemiology of CRKP

Geographic Distribution and High-Risk Areas for CRKP Infections

Because Carbapenem-resistant *K. pneumoniae* (CRKP) can cause severe infections that are challenging to treat, its global spread has grown to be a serious public health concern. At first, CRKP was mostly identified in areas where antibiotics were widely used, especially in healthcare facilities like hospitals & intensive care facilities (Sundararajan et al., 2020). Nevertheless, its global incidence has been rising during the past few years. Regional differences in CRKP distribution mean that certain regions report higher resistance rates than other (Peirano et al., 2021).

Hospitals in North America, notably the United States, are becoming increasingly concerned with CRKP, especially in urban regions where there are many congested hospitals. Recent findings show that often in individuals who have had extended hospital stays or invasive treatments, CRKP is most frequently detected in healthcare-associated diseases including bloodstream infections and pneumonia (Gandhi et al., 2020). Because of its resistance to almost all antibiotics, including carbapenems, and the substantial difficulties it causes in treatment, the CDC has classified CRKP as a "serious threat" to public health (CDC, 2019).

Carbacenem resistance in *K. pneumoniae* strains is common in several European countries, including

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Turkey, Greece, and Italy. Surveillance studies have revealed that hospital outbreaks of CRKP are more prevalent in these areas, mostly as a result of poor infection control policies, high rates of antibiotic usage, and a lack of efficient antimicrobial stewardship initiatives (Almasoud et al., 2021). India, China, and Pakistan are among the countries in Asia where the rapid spread of resistant strains has been exacerbated by the unregulated use of antibiotics and weak infection control practices in hospitals. Consequently, CRKP has reached alarming levels. Further complicating efforts to prevent its spread, CRKP is now discovered in community-acquired infections in certain parts of Asia in addition to hospital-acquired infections (Tumbarello et al., 2020). Moreover, CRKP transmission is more likely to occur in low- and middle-income nations since they do not have the resources to adequately fight antibiotic resistance (Zong et al., 2020).

Outbreaks and Epidemiological Data from Different Regions

A number of variables influence the CRKP infection epidemiology, such as healthcare practices, antibiotic availability and usage, and geographical differences in infection control methods. Outbreaks of CRKP are most common in healthcare settings, where the bacterium can spread quickly amongst patients, particularly those with compromised immune systems or undergoing invasive operations (Sundararajan et al., 2020).

According to the CDC, a considerable amount of multidrug-resistant infections in hospitals in the US are caused by CRKP, and the disease is also becoming more common in bloodstream infections and pneumonia. The incidence of CRKP between *K. pneumoniae* isolates present in hospital-associated infections increased from 0.6% in 2008 to 6.0% in 2017, according to the findings of a study that was carried out in the United States. These findings emphasise the necessity of strict infection control methods and the growing threat posed by CRKP (Gandhi et al., 2020).

Through the European Antimicrobial Resistant Surveillance Network (EARS-Net), the European Centre for Disease Prevention and Control, or ECDC, monitors the spread of CRKP throughout Europe. The use of carbapenems within hospitals is one factor leading to the increasing prevalence of CRKP, and hospital outbreaks are frequent, especially in countries with insufficient infection control procedures (Almasoud et al., 2021).

CRKP in Asia presents a major public health concern. According to studies conducted in China and India, there have been reports of extensive hospital outbreaks and a 40–50% incidence of resistant to carbapenem in *K. pneumoniae* isolates. A national study in India found that almost 70% of *K. pneumoniae* strains found in bloodstream infections were not sensitive to carbapenems (Tumbarello et al., 2020). Antibiotics are used too much and in the wrong way in both human and animal treatment, which is one reason for these high rates of resistance. Poor sanitation, insufficient measures to prevent infections, and the uncontrolled selling of antibiotics all contribute to the fast spread of CRKP in Asia and the emergence of resistance strains in both hospitals and community settings (Zong et al., 2020).

The Role of Travel and International Healthcare in the Spread of CRKP

Although it is most common in some areas, CRKP is spreading to other areas as well. The spread of resistant strains around the world has been facilitated by travel and treatment provided on an international scale.

Another important component in the transmission of CRKP is the mobility of healthcare personnel. Many healthcare professionals work abroad for medical missions or jobs, and the mobility of these professionals between nations with varying degrees of antibiotic resistance can help to propagate resistant organisms worldwide. As healthcare personnel may unknowingly transport pathogens with resistance genes from one nation to another, attempts to contain the spread of CRKP can be further complicated (Zong et al., 2020).

Another factor in the worldwide expansion of CRKP is the transportation of strains that are resistant from areas with a high frequency of the disease, which is facilitated by international travel. As an example, individuals from places like Pakistan or India who have a high CRKP frequency may bring resistant strains of *K. pneumoniae* back with them when they return home. These patients may then infect others,

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which could cause hospital outbreaks in places where CRKP wasn't common before (Tumbarello et al., 2020).

Additionally, patients are increasingly exposed to healthcare systems with inadequate infection control procedures and high antibiotic usage as a result of the growth of medical tourism, in which individuals travel overseas in search of less expensive medical care. According to Gandhi et al. (2020), this raises the risk of contracting CRKP infections while undergoing medical operations overseas and adds to the worldwide spread of resistance.

A complex problem, the global spread of CRKP is impacted by social, medical, and geographic variables. High-risk areas for CRKP include those with high levels of antibiotic usage, inadequate infection control procedures, and low resources to fight antimicrobial resistance. The spread of CRKP is different in different areas, and most cases happen in hospitals and other health care settings. Additionally, the global spread of CRKP has been greatly aided by travel and international medical treatment, underscoring the necessity of a concerted global effort to deal with this major public health concern. Prevention efforts against CRKP should centre on tightening up infection control measures, being more careful with antibiotics, and keeping an eye on the disease all across the world (Peirano et al., 2021).

Strategies to Combat CRKP

Antimicrobial Stewardship Programs

ASP programs constitute essential tools to fight CRKP resistance by ensuring antibiotics receive proper usage for intended duration and target pathogens effectively. The main focus of an ASP involves maximizing antibiotic use through controlling improper prescriptions while guaranteeing correct dosages and proper medication periods (Bassetti et al., 2021). Through precise management of broad-spectrum antibiotics such as carbapenems and other β-lactams ASP programs reduce the conditions which promote bacterial resistance development of CRKP.

The main reason for bacterial antibiotic resistance stems largely from medicinal antibiotic overuse. A variety of antibiotic prescribing errors takes place when health professionals prescribe antibiotics for viral infections or prescribe broad-spectrum drugs for narrow-spectrum infections or use antibiotics for extended durations (Peirano et al., 2021). As a part of their strategy ASPs provide education and perform audits to direct clinical practice toward pathogen-based antibiotic use after microbiological tests reveal infection sources. De-escalation of therapy is encouraged by ASPs by moving from carbapenems to more narrow-spectrum antibiotics after identifying pathogens and completing susceptibility tests (Gandhi et al., 2020).

Through optimized antibiotic prescribing activities ASPs cut down CRKP infection occurrences and defend current antibiotics effectiveness while moderating antibiotic resistance formation. Evidence confirms that hospitals implementing robust antimicrobial stewardship programs record better patient outcomes through reduced antibiotic-resistant infections together with diminished death rates and decreased healthcare expenses (Zong et al., 2020).

Infection Control Measures

Healthcare facilities must prioritize infection control strategies because they hold essential power to stop CRKP transmission. CRKP transmission remains high throughout healthcare facilities and intensive care units so hospitals must use strict infection control protocols to stop unwanted pathogen spread and hospital-acquired infections. The following measures serve as proper infection control protocols:

a. Hand Hygiene

Hand hygiene stands as the most crucial and efficient way to stop CRKP transmission along with other bacterial resistances from spreading. The successful prevention of CRKP transmission requires healthcare professionals to perform complete hand washes before encountering patients and afterward as well as when working with clinical tools (Pittet et al., 2020). People should use alcohol-based hand sanitizers instead of soap and water when those means are unavailable since these sanitizers can destroy several types of pathogens (Kampf et al., 2020).

b. Patient Isolation

Healthcare professionals must place CRKP-infected patients in isolation because the spread of resistant

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bacteria threatens other patients in treatment. Healthcare settings should use private rooms together with cohorting patients with the same infection and restrict movement of infected patients in accordance with guidelines (Zhou et al., 2020). Complete isolation protocols should apply to healthcare staff who need to wear proper personal protective equipment (PPE) including gloves, gowns and face shields when treating infected patients (Kassis et al., 2021).

c. Sterilization Protocols

Healthcare professionals must place CRKP-infected patients in isolation because the spread of resistant bacteria threatens other patients in treatment. Healthcare settings should use private rooms together with cohorting patients with the same infection and restrict movement of infected patients in accordance with guidelines (Zhou et al., 2020). Complete isolation protocols should apply to healthcare staff who need to wear proper personal protective equipment (PPE) including gloves, gowns and face shields when treating infected patients (Kassis et al., 2021).

d. Environmental Cleaning

Hospitals need established cleaning procedures to prevent CRKP from spreading through their environment. The hospital cleaning process includes daily cleaning of patient rooms together with common areas and equipment with special attention given to disinfecting surfaces that touch patients (Peirano et al., 2021). These infection control measures implemented with regularity demonstrate substantial power to decrease CRKP transmission and stop outbreaks within healthcare facilities (Zong et al., 2020). High levels of hygiene and prevention require regular employee training and infection control practice monitoring to maintain proper standards (Sundararajan et al., 2020).

The Importance of Monitoring and Tracking CRKP Prevalence in Hospitals and Healthcare Settings

Hospital CRKP surveillance remains essential because it delivers immediate information about the extent and movement of *K. pneumoniae* along with its resistance traits in medical facilities. The tracking of CRKP infections helps healthcare institutions detect outbreaks promptly so they can use timely actions to stop additional infections from spreading according to Peirano et al., 2021. Medical facilities with active surveillance systems screen high-risk patient groups including hospital stay extensions along with immune-compromised individuals as well as people who required invasive medical treatments. Through laboratory testing surveillance healthcare providers can identify new antibiotic-resistant strains which helps them make appropriate antibiotic therapy choices (Tumbarello et al., 2020).

Patient sample testing as well as evaluation of patient mobility and infection transmission patterns should be used for ongoing surveillance in healthcare facilities. The collected information enables the development of better infection control procedures and antimicrobial stewardship programs as well as providing evidence for developing superior infection prevention methods (Gandhi et al., 2020). Healthcare providers can take immediate action to restrict infection spread through their strengthened understanding of CRKP transmission patterns and prevalence zones which surveillance methods reveal. The collected data allows public health managers to establish regional and national public health plans (Sundararajan et al., 2020).

Vaccines and Alternative Therapies

Research efforts to create vaccines and alternative treatments for Carbapenem-resistant *K. pneumoniae* (CRKP) demonstrates significant promise in the management of resistant pathogenic infection. Scientific research continues to develop vaccines against *K. pneumoniae* germs in general terms and carbapenem-resistant strains specifically (Bassetti et al., 2021). The vaccines hold essential importance for infection prevention especially within vulnerable groups that include immune-compromised patients combined with elderly persons and those with chronic medical conditions (Jiang et al., 2020). The medical community investigates two alternative treatment methods for CRKP infections through phage therapy and immunotherapy.

Phage therapy applies bacteriophages as viruses that recognize specific bacterial targets to perform bacterial destruction. The targeted bacterial elimination properties of phage therapy make it a

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promising treatment for multidrug-resistant pathogen infections including those caused by CRKP without disturbing healthy microbiota (Karthikeyan et al., 2020). Clinical trials currently test phage therapy's safety and effectiveness because the therapy remains at an experimental stage according to Leavitt et al., 2020.

Through immunotherapy patients receive antibodies together with immune-boosting agents to improve their bodies' infection-fighting capabilities. Current scientific research for monoclonal antibodies and other immunotherapies reveals effective solutions which either block bacterial toxins or stimulate immune defenses against bacterial cells (Sotgiu et al., 2020).

Researchers are actively working on two fronts to create new antibiotics and adjuvants which surpass CRKP resistance factors. The emerging therapeutic alternatives seek to bring back effectiveness to carbapenems and additional antibiotics which resistance makes ineffective (Maziade et al., 2020). Antibiotic resistance evolution demands the development of innovative disease management treatments for CRKP infections.

Combating Carbapenem-resistant *K. pneumoniae* (CRKP) demands systematic methods which integrate antimicrobial management plans with strong infection prevention protocols as well as internal pathogen tracking and fresh medical treatments. Doctors must improve their antibiotic use both to stop unneeded drug resistance and to block CRKP spread in healthcare environments (Bassetti et al., 2021). The acquisition of CRKP distribution information through surveillance systems allows healthcare providers to make timely decisions that stop the spread of the outbreak. The development of vaccines and alternate therapies shows potential in decreasing CRKP infections while providing superior treatment alternatives to affected patients according to Tumbarello et al., 2020. The simultaneous use of these strategies represents an essential global approach to combat increasing CRKP infections and other multidrug-resistant infections.

Challenges and Limitations in Addressing CRKP

Limitations in Current Diagnostic Methods for CRKP Detection

Current diagnosis methods for Carbapenem-resistant *K. pneumoniae* (CRKP) infections present major obstacles in their ability to detect the pathogen effectively. The timely diagnosis of CRKP establishes fundamental requirements for stopping the infection's dissemination as well as administering proper medical care to patients. Various elements contribute to making CRKP detection difficult in healthcare environments. The results obtained through traditional culture-based methods require several days to emerge although these methods deliver accurate outcomes yet they cause delays in starting proper therapeutic measures. The resulting holdup substantially affects critically ill patients because they need urgent medical intervention (Kumarasamy et al., 2020).

Polymerase chain reaction (PCR) methods enable the detection of carbapenemase genes (KPC, NDM, OXA-48) although these methods are rarely accessible through resources limited healthcare systems. PCR tests come with financial challenges and the need for special equipment as well as limited applicability for standard clinical practice (Sharma et al., 2020). Phenotypic testing methods through susceptibility testing take extended periods of time while simultaneously producing inconsistent outcomes when detecting carbapenem resistance. The diagnostic complexities prevent timely accurate identification of CRKP which enables resistant strains to internationally spread throughout healthcare environments (Chakraborty et al., 2021).

Different healthcare facilities and geographical regions use inconsistent CRKP detection methods because no universal diagnostic protocols have been established. The creation of affordable rapid diagnostic equipment stands vital to authenticate early CRKP identification and shape correct treatment choices and obstruct CRKP transmission (Sotgiu et al., 2021).

Barriers to Effective Antimicrobial Stewardship in Low- and Middle-Income Countries

Several obstacles within low- and middle-income countries make it difficult to carry out effective antimicrobial stewardship programs which

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contributes to the increasing threat of CRKP. The main obstacle arises from antibiotic misuse that occurs because regulatory systems are absent or ineffective throughout many regions. LMICs have a practice of selling antibiotics including carbapenems without prescription which results in patients self-medicating together with improper antibiotic use. The excessive use of antibiotics across various healthcare settings increases the rate at which resistance forms including those against CRKP (Amin et al., 2021).

The insufficient healthcare infrastructure creates a major hurdle for implementing antimicrobial stewardship programs in Low-& Middle-Income Countries. Medical facilities in these regions struggle to create full-database stewardship programs because they do not have enough trained staff members so they have trouble getting diagnostic tests and lack adequate information about regional resistance patterns (Arias et al., 2020). The insufficient infrastructure hinders antibiotic usage tracking and resistance pattern monitoring as well as creating obstacles to execute proper infection control procedures (Ali et al., 2021).

The implementation of antimicrobial stewardship programs faces hurdles because of insufficient budgetary support from government entities. LMIC healthcare systems choose to deliver immediate patient care above long-term infection prevention and control plans thus making it hard to create funding for stewardship initiatives (Sotgiu et al., 2021). Health professional workers in these locations commonly lack complete antimicrobial stewardship education and lack proper knowledge about the harmful consequences of excessive carbapenem use. The elimination of these barriers requires ongoing international backing and enhanced healthcare infrastructure funds together with training sessions aimed at both healthcare professionals and the public population (Koh et al., 2021).

The Need for International Collaboration to Address the Growing Threat of CRKP

The challenge of spreading CRKP features as a worldwide issue which crosses international borders which demands joint work among nations. Countries where CRKP infections are common provide a foundation that releases drug-resistant bacterial strains which propagate into different regions because of international travel, movement of people and market exchanges (Peirano et al., 2021). The combat against CRKP depends heavily on worldwide cooperation.

There is a global requirement for surveillance systems to monitor the spreading patterns of CRKP alongside other multidrug-resistant organisms. The World Health Organization (WHO) and various international organizations maintain that nations should enhance their support for worldwide surveillance systems and research data repository collaboration. Countries engaged in joint efforts will enhance their understanding of CRKP
and will benefit from mutual best-practice sharing as well as modern treatment option and vaccine development (Zong et al., 2020). International programs must establish standardized diagnostic methods and enhance antimicrobial stewardship and offer technical support to developing nations (Tumbarello et al., 2020).

The global fight against CRKP needs worldwide participation for researching and developing fresh antibiotics together with therapeutic options. In response to antibiotic-resistant infections pharmaceutical companies need to combine forces with national governments as well as international organizations to deliver fresh therapies for resistant bacteria. The joint effort of researchers accelerates development of innovative therapeutic solutions and vaccine-based approaches for treating CRKP as well as other resistant pathogens (Bassetti et al., 2021).

Resistance Mechanisms That Continue to Evolve, Complicating Treatment Strategies

The continuing development of resistance mechanisms among *K. pneumoniae* infections makes therapeutic treatments more complex thereby creating ongoing difficulties when managing CRKP infections. *K. pneumoniae* evolves by combining multiple resistant mechanisms which creates situations of both multidrug resistance and pan-resistance (Peirano et al., 2021). These resistance mechanisms work by changing external membrane porins to block antibiotics and creating extra efflux pumps to remove antibiotics but also generate more beta-lactamases that destroy various antibiotics (Sotgiu et al., 2021).

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K. pneumoniae continues to evolve through its development of new resistance mechanisms which could make polymyxins and all other available antibiotics useless. The emergence of colistin-resistant *K. pneumoniae* strains has been detected in specific areas according to Zong et al. (2020) which obstructs CRKP infection treatment. Medical professionals currently possess limited alternatives for treating infections since resistance against antibiotic classes used as final treatment options remains a major health issue. The combination of resistance genes in *K. pneumoniae* happens quickly through horizontal gene transfer because of plasmids and transposons and integrons (Tumbarello et al., 2020). The capacity to exchange resistance genes fosters resistance spread at a rapid pace which hinders the creation of effective treatment strategies (Bassetti et al., 2021).

Ongoing resistance mechanisms' evolutionary patterns necessitate constant safety protocols and continuous antibiotic development studies and updated treatment protocols for the changing patterns of antimicrobial resistance. The management of Carbapenem-resistant *K. pneumoniae* (CRKP) encounters various obstacles between diagnostic hindrances and antimicrobial stewardship restrictions and active resistance mechanism adaptation. Successful resolution of these problems needs consistent cooperation among international governments together with government bodies and community groups. Public health will suffer from the spread of CRKP unless surveillance programs intensify alongside the creation of new treatment options with global collaboration between health authorities (Koh et al., 2021). The challenge of defeating CRKP in low- and middle-income countries depends on the implementation of stewardship programs and international collaboration alongside overcoming antibiotic barriers (Sundararajan et al., 2020).

Conclusion

The development and dissemination of Carbapenem-resistant *K. pneumoniae* (CRKP) and the variables that have contributed to this worldwide threat. The development of CRKP is driven in large part by antibiotic exposure, especially the abuse and misuse of carbapenems and other broad-spectrum antibiotics. Additionally, we discovered that the main factors leading to the spread of CRKP include conditions in hospitals and intensive care units, extended antibiotic treatment, and insufficient efforts to prevent the spread of infections. The review also found many *K. pneumoniae* resistance mechanisms—including carbapenemase synthesis, porin channel alterations, efflux pumps, and beta-lactamase overproduction—that together complicate treatment methods. This problem is made worse by the fact that resistance mechanisms are constantly changing and that diagnostic techniques are difficult. The study at last emphasised the importance of ongoing research, monitoring, and international cooperation to handle the rising CRKP threat.

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