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Review Article

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# Resistance mechanisms, control strategies and outbreak management in *Klebsiella pneumoniae*

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## ABSTRACT

*Klebsiella (K.) pneumoniae* is a major reason of multidrug-resistant infections worldwide. The Enterobacterales that produce β-lactamases represent significant sources of infections within healthcare environments. This prevalence can be attributed to the challenges they pose in treatment, their high potential for transmission, and their substantial economic and personal impact. Recent studies highlight the emergence of multidrug-resistant *K. pneumoniae* strains which show resistance to colistin, a last-line antibiotic, arising from mutational inactivation of the *mgrB* regulatory gene. The bacteria of greatest clinical relevance are those with resistance to third and fourth generation cephalosporins, extended spectrum β-lactamases and ampicillin-cephalosporin. Carbapenems represent a category of antibiotics that remain one of the limited options for addressing infections caused by multi-drug resistant pathogens. Typically, these antibiotics are reserved as a final solution when other therapies prove ineffective. Nevertheless, the rising prevalence of carbapenem-resistant bacteria presents a considerable obstacle to their efficacy. Continuous monitoring and the advancement of alternative therapeutic strategies are essential to tackle the escalating challenge of antibiotic resistance. However, the rise of carbapenem-resistant Enterobacterales poses significant health challenges. Notably, *K. pneumoniae*, a pan-resistant bacterium, is associated with high morbidity rates, particularly in public health settings. This study reviews the various aspects of antibacterial resistance, focusing on the genes present in the genome of *K. pneumoniae* and the mechanisms through which it develops resistance. Through the analysis of these factors, we intend to highlight the escalating threat posed by antibiotic resistance and the urgent requirement for effective measures to counteract it. Surveillance and diagnostics are vital for controlling outbreaks as they enable early detection of diseases, allowing for timely interventions to prevent further spread. Accurate laboratory diagnostics are essential for confirming cases and informing public health responses, thereby ensuring the effective allocation of resources during an outbreak.In this work, we have carried out a review on the antibacterial resistance antibiotics, genes found in its genome, as well as the resistance mechanisms involved. Finally, we focus on the main outbreaks causing hospital acquired infections during the last few years.

**KEYWORDS:** *Klebsiella pneumoniae;* Antibiotic resistance; Carbapenem resistance; Resistance mechanisms

## 1. Introduction

*Klebsiella (K.) pneumoniae* is an encapsulated Gram-negative *bacillus* belonging to the family Enterobacterales. It was first discovered in 1882 by Carl Friedlander[1], from lung tissues of dead pneumonia patients. It presents a mucoid phenotype in culture media such as MacConkey or eosin methylene blue agars. Also, it is capable of fermenting lactose and mannitol, and reducing nitrate

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to nitrite. *K. pneumoniae* is a bacterium able to infect humans, causing different kinds of infections, including urinary tract and respiratory infections, soft tissue infections, surgical wounds and sepsis. After *Escherichia coli*, *K. pneumoniae* is the second most important opportunistic enterobacterium causing hospital acquired infections and community infections[1]. Hospital-acquired infections (HAIs) also known as healthcare-associated infections are infections that occur after a patient has been admitted to a hospital or healthcare facility and were not present at the time of admission. These infections typically manifest more than 48 hours after the patient has been admitted, distinguishing them from pre-existing conditions.

The pangenome of *K. pneumoniae* (total set of genes) is approximately 5.5 Mbp in size and codes for an average of 5 500 genes. More than 30 000 distinctive sequences have been recognizing that code for different proteins. However, it is still an open pangenome, in which there are extra genes that have not yet been characterized[1,2]. Its core genome (set of genes shared by all members of the species) is composed of approximately 2 000 genes. These genes have been set on by examining their presence in more than 95% of the isolates from that species[1,2].

*K. pneumoniae* is a significant contributor to the global crisis of antimicrobial resistance, with mechanisms such as enzymatic antibiotic inactivation, target alteration, and biofilm formation leading to its multidrug-resistant (MDR) status[3]. The global burden of *K. pneumoniae* infections is alarming, with estimates indicating that it causes over 90 000 infections and approximately 7 000 deaths annually in Europe alone, highlighting the urgent need for effective control measures and innovative therapeutic strategies to combat this public health threat[4].

The additional genome carries genes that vary between bacteria of the same species. These involve both chromosomally encoded genes and those located in the mobile genetic elements. In *K. pneumoniae*, most of the genome is made up of accessory genes. This allows their classification into different strains and different pathotypes can be catalogued in the clinical setting [opportunistic, carbapenem-resistant enterobacterales (CRE) or hypervirulent (hv) bacteria] (Figure 1)[1].

These accessory genes to form new pathotypes (hvCRE) as they can be shared between species by transfer of horizontal genetic material[1,2]. Therefore, the accessory genomes disclose the virulence of a bacterium and its study is needed to understand the clinical characteristic of an infectious disease. Moreover, this type of genome can develop due to the different changes occur in the genome of the pathogen, or by the accession of new genes for resistance or variation in its expression[5]. The high number of genes encoding for β-lactamases prove that they are crucial to the antibiotic resistance.

Over the last few decades, *K. pneumoniae* has come into a wide variety of antibiotic resistance mechanisms and, thus, the nosocomial infections or HAIs casused are particularly

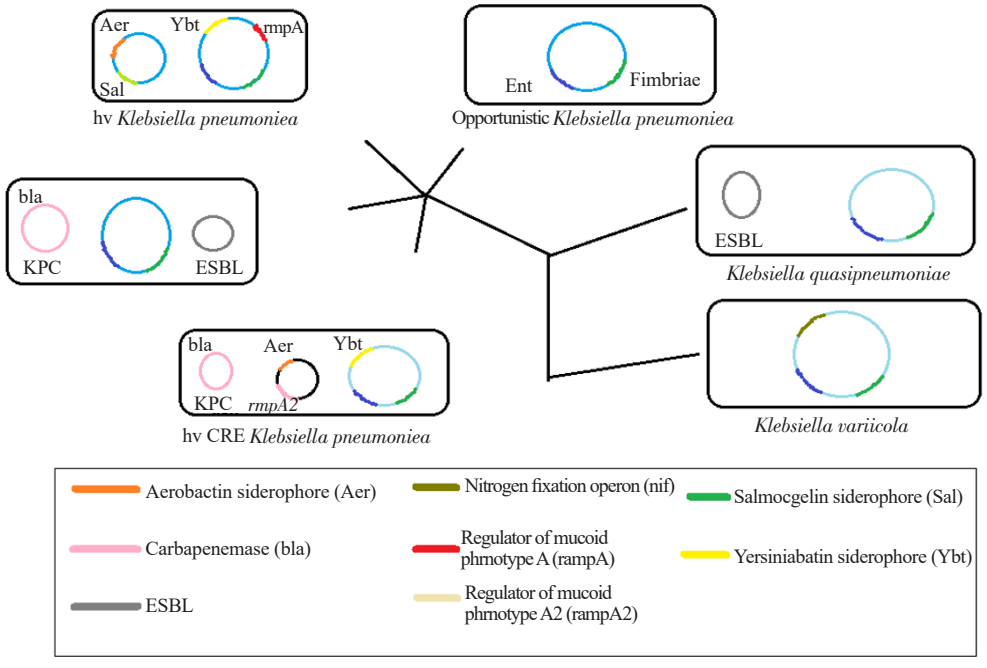



**Figure 1.** Shared accessory genes in *Klebsiella pneumoniae*, *Klebsiella variicola* and *Klebsiella quasipneumoniae*. Enterobactin (blue) and Fimbriae (dark green) as conserved genes[1].

problematic. This increases the difficulty of detecting resistant strains and gives the suitable treatment for each bacterium. In a healthcare center, there are several potential foci that facilitate the transmission of *K. pneumoniae* including person-to-person contact between health workers and patients, contaminated surfaces, instrumentation, and some medical techniques (endoscopy) *etc*. Diseases that decrease the immunity of the patient, such as cancer, some neurological disorders, diabetes mellitus, or electrolyte and fluid disorders may be categorize as risk factors for infection. Although *K. pneumoniae* is a component of the normal intestinal flora, it has the capability to colonize various mucosal surfaces, such as the urinary and gastrointestinal tracts, as well as the nasopharynx. This can lead to severe infectious diseases, particularly in immunocompromised individuals[1].

## 2. Metallo β–lactamases

Metallo β-lactamases are a diverse group of metalloenzymes that have the ability to hydrolyze nearly all β-lactam antibiotics except monobactams and they are not susceptible to inhibition by commercially available β-lactamase inhibitors like sulbactam, tazobactam, or clavulanic acid[6,7]. Also they are not inhibited by NXL-104 that are active against β-lactamase enzymes of class A and C. Because of zinc utilization, metal chelators like ethylene diamine tetra acetic acid can inhibit their activity[7]. Class B β-lactamases (MBLs) have a common αβ/βα sandwich fold and a metal-binding motif located at the interface of two αβ domains[8].

New Delhi metallo-β-lactamase (NDM) is a type of metallo-MBL able to hydrolyze most β-lactamase also including carbapenems but not monobactams[9,10]. NDM has poor activity against amdinocillin, an extended-spectrum penicillin antibiotic of the amidinopenicillin family[11]. *blaNDM–1* gene was describe from *K. pneumoniae* and *Escherichia coli* strains in 2008 for the first time from a patient suffering from urinary tract infections in New Delhi, it has been identified with higher frequency among Enterobacteriaceae family in India, then later reported in bacterial strains around the world[10].

## 3. Resistance mechanisms in *K. pneumoniae*

*K. pneumoniae* exhibits resistance to other families of antibiotics. Most of these antibiotic resistance mechanisms have been acquired through horizontal gene transfer, conferring a high level of resistance to antibiotics such as β-lactams and quinolones.

### 3.1. β–lactam antibiotics resistance mechanisms

One of the resistance mechanisms in *K. pneumoniae* includes the alteration of penicillin binding proteins (PBPs), enzymes that catalyze peptidoglycan synthesis and particular target of the β-lactam antibiotics. The modifications in their structure reduce the affinity of PBPs for the β-lactam antibiotics, increasing resistance to them[12,13]. β-lactam antibiotics act by inhibiting the bacterial cell wall biosynthesis; they are the most accessible antibiotics which treat a various number of bacterial infections(Figure 2). For having a global positive impact on health by treating bacterial infections, penicillin and other β-lactam antibiotics are probably the most important drugs ever[14]. β-lactams are effective against a wide range of bacteria and exhibit minimal toxicity to humans[15]. However, the emergence of resistance to these antibiotics poses a significant challenge, as bacteria and other pathogens have evolved various mechanisms to evade the effects of antibiotics and other antimicrobial agents. Moreover, outer membrane permeability modifications are critical in *K. pneumoniae* resistance (hydrophilic drugs). The outer membrane is a barrier that must be crossed before it can bind to PBPs[13]. The molecules of antibiotic must use the porins (*OmpK35* and *OmpK36*), which bring down the number or modify, reduce the permeability of the membrane[12,16]. The common mechanism in *K. pneumoniae* strains are active ejection pumps like *AcrAB* and *OqxAB*[12].

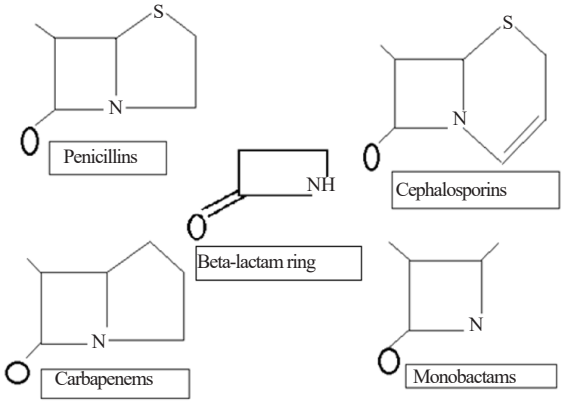



**Figure 2.** Mechanisms of action of β-lactam antibiotics.

### 3.2. Quinolone resistance mechanism

Mechanisms of fluoroquinolone resistance are due to point mutations in specific areas of DNA gyrase (genes *gyrA* and *gyrB*) and topoisomerase IV (genes *parC* and *parE*), which are referred to as quinolone resistance determining region. The first target for quinolone resistance in Gram-negative micro-organisms is *gyrA* and then *parC*. Quinolones target bacterial topoisomerases,

blocking bacterial DNA replication. These drugs have been used in clinical practice since the 1960s, but their use increased extensively after the introduction of the first fluoroquinolones in the 1980s, which had led to development of bacterial quinolone resistance mechanisms[17].

Several simultaneous mutations in these genes increase high level resistance[18]. In addition, resistance mechanisms are acquired through mobile genetic elements, such as the acquisition of quinolone resistance proteins that protect DNA gyrase and topoisomerase IV. Altered permeability and the presence of efflux pumps are also mechanisms involved in quinolone resistance[19,20]. Changes in *K. pneumoniae* cell permeability have been reported to be involved in quinolone resistance, similar to their role in β-lactam resistance. These included *OmpK36* deficiency, over expression of *acrAB*, the multidrug efflux pump gene and unaltered production of *kdeA*[21–23].

## 4. Hospital infection–control measures

HAIs are infections that occur more than 48 hours post-admission. HAIs are caused by viral, bacterial, and fungal pathogens. An important predisposing factor to HAIs is the use of instrumentation or devices for intubation, delivery of therapeutic agents, or drainage of body fluids during patient care as supportive measures. Infection control professionals collect data on device-related infections, *i.e.* catheter-associated urinary tract infections, vascular catheter-associated infections, and ventilator-associated pneumonias. Unlike other HAIs, device-related infections are linked directly to medical care. According to the National Nosocomial Infection Surveillance Report, in 2006, 8 833 device-related infections in adults were reported from participating healthcare facilities[14]. There were 3 759 catheter-associated urinary tract infections reported from 433 locations. Catheter-associated urinary tract infections accounted for most of the infections. There were 2 681 vascular catheter-associated infections reported and 2 393 ventilator-associated pneumonias from 548 locations[14,15].

Infection control measures, such as staff training, strict contact prevention, and thorough cleaning of the hospital environment and medical devices (like aspirator heads and ventilator surfaces), were implemented in ICUs. Also cleaning, hand hygiene and disinfection training programs, such as good cleaning of the patient's surrounding, wearing clean aprons during the dispensing of clean materials, wearing aprons and preparing clean materials for the preparation of new patient beds, were created to educate staff. During the staff work, observation and feedback were taken by the committee nurse. Further, awareness created in staff by training about the importance of carbapenem resistance *K. pneumonia*e and its infections.

## 5. *K. pneumoniae* resistant strains outbreaks

*K. pneumoniae* is considered one of the most important opportunistic pathogens in both community and nosocomial infections. More than 100 different antibiotic resistance acquired genes have been identified in *K. pneumoniae*[24,25]. The presence of SHV-1 penicillinase on the chromosome confers intrinsic resistance to ampicillin, amoxicillin and ticarcillin[2]. Resistance of enterobacteria to the β-lactam antibiotics is associated to the presence of genes encoding for β-lactamases[2,5]. These β-lactamases are frequently encoded by the *bla* genes and are part of the CTX-M, TEM, SHV and OXA families, sharing different hydrolytic profiles[2]. In the TEM family, mutations of individual nucleotides in genes encoding β-lactamases of the TEM-1 type change the phenotype of extended-spectrum beta-lactamase (ESBL). A wide diversity of members of the TEM family is known, which facilitates the search for transmission of individual resistance genes between strains[2,26]. The amino acid sequence of the SHV-1 family has a high rate of coincidence with TEM-1, sharing its molecular structure. The CTX-M family shows greater activity against cefotaximes than cephtazidime (third-generation cephalosporins), because of the geometry of the antibiotic binding site, which allows efficient recognition of cefotaxime, but not of cephtazidime (a larger molecule). The CTX-M producing strains have the same clinical implications as the production of other ESBL. Nowadays, the number of variants of this family is increasing[2,26]. The CTX-M family shows greater activity against cefotaximes than cephtazidime (third-generation cephalosporins), because of the geometry of the antibiotic binding site, which allows efficient recognition of cefotaxime, but not of cephtazidime (a larger molecule). OXA-48 producing *K. pneumoniae* is dangerously common in healthcare centers. These are the strains that cause most of the bacteremia outbreaks in hospitals throughout Europe and the Middle East.

## 6. *K. pneumoniae* outbreaks management

### *6.1. Rapid diagnosis*

Hospitals are increasingly using molecular diagnostic techniques, such as polymerase chain reaction (PCR) and whole-genome sequencing (WGS), to quickly identify *K. pneumoniae* strains and

their resistance profiles. These methods enable the rapid detection of specific resistance genes, facilitating timely treatment decisions and effective infection control measures[27]. Regular screening of patients through rectal surveillance cultures has become a common practice in many healthcare settings. This proactive approach is essential for identifying asymptomatically colonized individuals, which plays a crucial role in preventing the spread of infections within hospitals[27,28].

### 6.2. Infection control protocols

Infection control measures for *K. pneumoniae* involve a combination of strategies to prevent the spread of the bacteria in healthcare settings. Standard and transmission-based precautions, including the use of personal protective equipment such as gloves, masks, and gowns, are essential to minimize transmission risks. Cohorting patients and implementing isolation protocols ensure that infected individuals are separated from others, reducing the risk of cross-contamination. Continuous staff training on proper use of personal protective equipment, cleaning procedures and patient management is crucial, along with providing the necessary resources to support infection control efforts. Education on infection prevention and control strategies further empowers healthcare providers to adhere to best practices while proper hand hygiene remains one of the most effective methods to prevent the spread of infection.

### 6.3. The European Commission and the European Centre for Disease Prevention and Control (ECDC)

The ECDC have proposed to increase surveillance and control of outbreaks, in order to reduce the impact of infectious diseases caused by multi-drug resistant organisms on the population[2,26,29]. *K. pneumoniae* resistant strains to multiple drugs are being more frequently isolated, and this leads to the phenotyping techniques becoming little sensitive or unspecific, making it difficult to identify the strain causing the nosocomial disease.

Table 1 shows the main families of plasmids that confer resistance to clinically relevant antibiotics, such as extended spectrum cephalosporins, fluoroquinolones and aminoglycosides. The number of references obtained for TEM, KPC and CTX-M type enzymes is very high compared to the rest of the enzymes, supporting their importance for the health field and the scientific community. In the 1970s, most outbreaks of HAIs caused by *K. pneumoniae* were due to aminoglycoside resistant strains. Between 1990 and 2000, outbreaks caused by ESBL-producing strains were described, while those caused by carbapenemic resistant strains were described from 2000 onwards. Today, strains producing carbapenemics such as KPC and NDM-1, are significant in clinical practice[29].

*K. pneumoniae* NDM-1, a zinc-dependent metallo-β-lactamase, was initially discovered in 2009 in a patient from New Delhi. This enzyme, attached to the outer membrane, has the ability to sequester zinc from the host. Furthermore, vesicles are capable of transporting the active NDM-1 enzyme through exocytosis.

**Table 1.** Review of resistant plasmid families associated with AmpC, BLEE, 16S rRNA methylases, Qnr proteins and MBLs in *K. pneumoniae*.

| Enzyme | Replicons | No. of plasmids | Gen-bank references |
|---|---|---|---|
| CMY-8 (CTX-M-3) | HI2 | 1 | 3 |
| CMY-36 | ColE | 1 | 7 |
| CTX-M-3 (ArmA) | L/M | 73 | 11 |
| | HI2 | 68 | - |
| CTX-M-14 | FII, FIB | 13 | 11 375 |
| CTX-M-15 [TEM-1, AAC(6′)-IB-CR | FII, FIA, FIB | 152 | 17 |
| | NT | 22 | |
| CTX-M-17 | ColE | 1 | 5 |
| CTX-M-62 | NT | 1 | 5 |
| | L/M | 118 | 397 |
| SHV-5 | FII, FIB | 2 | |
| | I1 | 12 | |
| | K | 5 | |
| SHV-12 | FII, FIB | 9 | 1 189 |
| | FIIK | 1 | |
| TEM-1 | ColE | 2 | 67 442 |
| | N | 1 | |
| KPC-2 | ColE | 1 | 29 077 |
| IMP-4 (QnrB2, QnrB-4, ArmA) | L/M | 22 | |
| | A/C | 15 | 18 888 |
| | I1 | 17 | |
| VIM-1 | N | 15 | 2 379 |
| | NT | 1 | |
| VIM-4 (CMY-4) ArmA | A/C | 2 | 5 |

As a result, it can interact with other bacteria and attach to their membranes, mimicking the expression of the enzyme in those bacteria and rendering them temporarily resistant. Additionally, the plasmid gene *bla*NMD-1 encodes NDM-1, which can be transferred to other strains through horizontal gene transfer. Strains that produce this enzyme are able to break down all β-lactam antibiotics, with the exception of aztreonam. Hesperidins have been found to exhibit strong activity against NDM-1 among the potential inhibitors studied. Because of their low toxicity, hesperidins are being considered as potential drugs to inhibit NDM-1[29].

## 7. Conclusions

The widespread and unrestricted use of antibiotics, especially those belonging to the β-lactam category, has played a significant role in the rapid rise of antimicrobial resistance. The growing incidence of HAIs linked to β-lactamase-producing enterobacteria, such as *K. pneumoniae*, has created a substantial economic burden globally due to the limitations on effective treatment options. The observed relationship between the administration of certain antimicrobial drugs and the resistance patterns in *K. pneumoniae* highlights the urgent need for coordinated efforts across various departments to ensure the responsible use of these medications. The focus should shift from merely expanding the therapeutic options to developing alternative approaches that reduce the direct use of antimicrobials, thus lessening the effects of MDR pathogens on the population. Addressing MDR *K. pneumoniae* requires urgent global action and cooperation. Countries must enhance surveillance systems and share data effectively to monitor resistance patterns. Implementing robust antimicrobial stewardship programs is essential to optimize antibiotic use and minimize resistance development. Collaborative efforts across healthcare, veterinary, and environmental sectors can significantly impact the fight against multidrug-resistant *K. pneumoniae*. Together, we can safeguard public health and preserve the effectiveness of antibiotics for future generations.

## Conflict of interest statement

The authors claim there is no conflict of interest.

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## Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

## Authors' contributions

Verma G conceptualized the review, interpreted the literature. Verma G and Sharma B contributed to the writing, critical review, and editing of the manuscript to ensure clarity, coherence, and scholarly rigor. All authors reviewed and approved the final version of the manuscript.

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