Journal of Community Health Provision
Vol. 6, Issue 1, 2026
Page 56-67
DOI: https://doi.org/10.55885/jchp.v6i1.914

Microbiological Characterization of KPC-Producing Klebsiella Pneumoniae: A Systematic Review

Aiman Idrus Alatas[1], Delly Chipta Lestari[2]

[1]Clinical Microbiology Specialist Program, Faculty of Medicine, Universitas Indonesia
[2]Microbiology Department, Faculty of Medicine, Universitas Indonesia
Email: ayman.alatas@gmail.com

Abstract. *Klebsiella pneumoniae (K. pneumoniae) is an opportunistic bacterium that causes nosocomial infections and usually affects people with malfunctioning immune systems. These bacteria can also cause potentially fatal community-acquired diseases. A high fatality rate has been documented in carbapenem-resistant K. pneumoniae, particularly carbapenemase-producing cases. This is due to few antibiotic therapy choices. This study aims to assess the microbiological characteristics of KPC-K. pneumoniae in terms of their genotypic features. This article reported a systematic review that used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to identify articles related to carbapenem-resistant K. pneumoniae. Pubmed and SagePub, two online databases, were searched using pre-established inclusion and exclusion criteria. The search turned up six studies that showed K. pneumoniae contains numerous gene mutations that cause carbapenem resistance, including blaKPC, blaKPC-2, blaKPC-3, and blaKPC-23. The mutations in porins OmpK35, OmpK36, and OmpK37 also significantly contribute to this resistance. These findings indicated that the optimal combination of antibiotics should be tailored to the specific strain of K. pneumoniae with a carbapenem-resistant genotype, especially for KPC-Kp strains with a mutation in OmpK36. The findings of this systematic review offer vital information for creating successful strategies to fight carbapenem-resistant K. pneumoniae infections.*

Keywords: *Antibiotics, Carbapenem-Resistant, Klebsiella Pneumoniae, KPC, Mutation*

Received: February 11, 2026 Received in Revised: March 23, 2026 Accepted: April 12, 2026

INTRODUCTION

Klebsiella pneumoniae, sometimes known as *K. pneumoniae*, is a major contributor to nosocomial infections (Mohd et al., 2021; Hu et al., 2021; Pitout et al., 2015). Primarily infecting immunocompromised patients, *Klebsiella pneumoniae* functions as a conditional pathogenic bacterium (Sahly et al., 2002; Martin & Bachman, 2018). Moreover, it may result in illnesses that people in the community pick up, which may kill otherwise healthy people. Meningitis, necrotizing fasciitis, endophthalmitis, and severe *pneumonia* are examples of these illnesses. *Pyogenic* liver abscesses are another (Luo et al., 2016).

Pathogenic *K. pneumoniae* serotypes that generate excessive amounts of capsule *polysaccharides* may be the source of these disorders (Ko, 2017; Follador et al., 2016; Ke et al., 2025; Tsai et al., 2023; Rendueles, 2020). In addition to producing capsule *polysaccharides*, *K. pneumoniae* also uses other virulence factors, such as *lipopolysaccharide*, *fimbriae*, proteins found in the outer membrane, and elements that affect the uptake of iron and nitrogen sources. These

factors collectively enable the bacterium to circumvent host immune defenses and maintain its survival during the course of infection (Li et al., 2014).

Carbapenems, including *imipenem* and *meropenem*, are regarded as the primary therapeutic option for managing life-threatening infections attributable to extended-spectrum *β-lactamase* (*ESBL*)–producing *Enterobacteriaceae* (Castanheira et al., 2021; Piper et al., 2019) thereby possibly putting pressure on those antibiotics to develop resistance. Although *β-lactam* agents remain the preferred therapy for infections due to *K. pneumoniae*, the prevalence of strains producing *β-lactamases*, particularly *carbapenemases*, has increased substantially (Karampatakis et al., 2023).

The synthesis of the enzyme *carbapenemase* is a well-known contributor to carbapenem resistance (Abou-assy et al., 2023). The earliest identified variants of *Klebsiella pneumoniae carbapenemase* (*KPC*), namely *KPC-2* and *KPC-3*, have achieved widespread global dissemination, particularly among *K. pneumoniae* isolates (Hobson et al., 2022; Falagas et al., 2025; Lee et al., 2016; Munoz-Price et al., 2013).

Although isolates producing *Klebsiella pneumoniae carbapenemase* (*KPC*) may appear phenotypically susceptible to *carbapenems*, their expanding global distribution has complicated both detection and clinical management (Tzouvelekis et al., 2012; Reyes et al., 2019; Mohammadpour et al., 2025; Alvisi et al., 2025). In many cases, *tigecycline* and *polymyxins* remain among the few remaining therapeutic options for these infections (Campos et al., 2016; Jin et al., 2021). Unfortunately, due to their *pharmacokinetic* characteristics and toxicity, therapeutic usage of these antimicrobials has been limited. Nevertheless, no novel antimicrobials exist in advanced clinical trials against these multidrug-resistant (MDR) microorganisms.

KPC-producing *Klebsiella pneumoniae* (*KPC–K. pneumoniae*) was first reported in the United States in 1996. Sporadic cases were observed initially, but a marked increase in isolation occurred in 2001 following multiple hospital outbreaks in the New York area. While KPC-*K.pneumoniae* has grown, it has regularly broken out of Israel, China, and Greece. Colombia was home to the first KPC-2-*K. pneumoniae* isolates discovered in South America in 2006 (Satlin et al., 2017).

Gram-negative bacteria, particularly *K. pneumoniae*, have rapidly spread across the globe (Songsantiphap, Vanichanan, Chatsuwan, Asawanonda, & Boontaveeyuwat, 2022). However, the precise epidemiology of these enzymes varies depending on the region and locale. Infections with positive KPC organisms have a high reported death rate, which may result from the limited antibiotic treatment choices currently available (often *colistin, tigecycline*, or *aminoglycosides*) (Gaibani et al., 2020).

Several studies assisted in conducting this research. Santino et al. (2013) reported that fifteen clinical isolates of *Klebsiella pneumoniae* exhibiting reduced susceptibility to *carbapenems* and resistance to *colistin* were obtained from a hospital in Italy. Marko and their friends conducted the same study through a nationwide survey. Jelic et al. (2016) reported that the initial dissemination of *KPC*-producing *K. pneumoniae* in Croatia was linked to a dominant *PFGE* type associated with sequence type *ST258*. An investigation by Yingying Du and colleagues focused on the genomic characterization of *KPC*-producing *Klebsiella pneumoniae* isolates obtained from the ICU of a teaching hospital in Shanghai, China.

Their findings indicated that resistance plasmids carrying conjugative transfer elements play a crucial role in the dissemination of antimicrobial resistance, while the *blaKPC-2* carbapenemase gene remains relatively conserved during evolutionary processes. Furthermore, the presence of *blaKPC-2* together with *fosA6* or *blaCTX-M* variants was linked to increased resistance to *fosfomycin* and to broad-spectrum *β-lactams*, respectively (Du et al., 2022). Those studies were reviewed by the method that the authors chose. However, recent studies have found a correlation between triple medicine combinations combining *colistin*, *tigecycline*, and *imipenem* and improved survival rates in individuals suffering from bacteremia (Songsantiphap et al., 2022).

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

METHODS

To ensure methodological rigor, this study followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Steps were adequately performed so the investigation findings could be trusted. This literature review sought to examine the microbiological characteristics of KPC–*K. pneumoniae* through the analysis of previously published studies on this topic. The review was designed to highlight key issues reported in the existing literature. Studies were considered eligible if they met the following criteria. First, the publication had to be written in English and specifically address the microbiological characterization of KPC-producing *K. pneumoniae*. Second, only articles published after 2013 and within the timeframe covered by this systematic review were included. Publications such as editorials, manuscripts without a DOI, previously published review articles, and records that were substantially similar to existing journal publications were excluded from the analysis. As keywords, we utilized "microbiological characterization," *"KPC-Producing*," and "*Klebsiella pneumoniae*." The search for papers that would qualify for the systematic review was conducted using the PubMed and Sage Pub databases on 17 February 2023 by entering the keywords: *(("microbiologic"[All Fields] OR "microbiologically"[All Fields] OR "microbiology"[MeSH Terms] OR "microbiology"[All Fields] OR "microbiological"[All Fields]) AND ("characterization"[All Fields] OR "characterizations"[All Fields] OR "characterize"[All Fields] OR "characterized"[All Fields] OR "characterizes"[All Fields] OR "characterizing"[All Fields] OR "characterization"[All Fields] OR "characterizations"[All Fields] OR "characterize"[All Fields] OR "characterized"[All Fields] OR "characterizes"[All Fields] OR "characterizing"[All Fields]) AND "KPC-Producing"[All Fields] AND ("klebsiella pneumoniae"[MeSH Terms] OR ("klebsiella"[All Fields] AND "pneumoniae"[All Fields]) OR "klebsiella pneumoniae"[All Fields])) AND ((y_10[Filter]) AND (ffrft[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))* used in searching the literature. Only studies that satisfied all predefined inclusion criteria were retained in order to ensure that the selected literature remained relevant to the objectives of this systematic review. Research that did not comply with these criteria was excluded from further consideration. After the screening process, the remaining studies were subjected to a comprehensive evaluation. During this stage, key information was extracted from each article, including the study title, authors, year of publication, geographical location, research procedures, and the parameters examined. Prior to determining which studies would proceed to further analysis, each author independently screened the titles and abstracts of the retrieved publications. Articles that met the predefined inclusion criteria were then assessed in full for eligibility in the systematic review. Based on this evaluation, the studies considered most appropriate were selected for inclusion. These criteria were applied to facilitate the identification of relevant manuscripts, to clarify the scope of previous research, and to determine which aspects of earlier investigations justified their inclusion in the review.

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

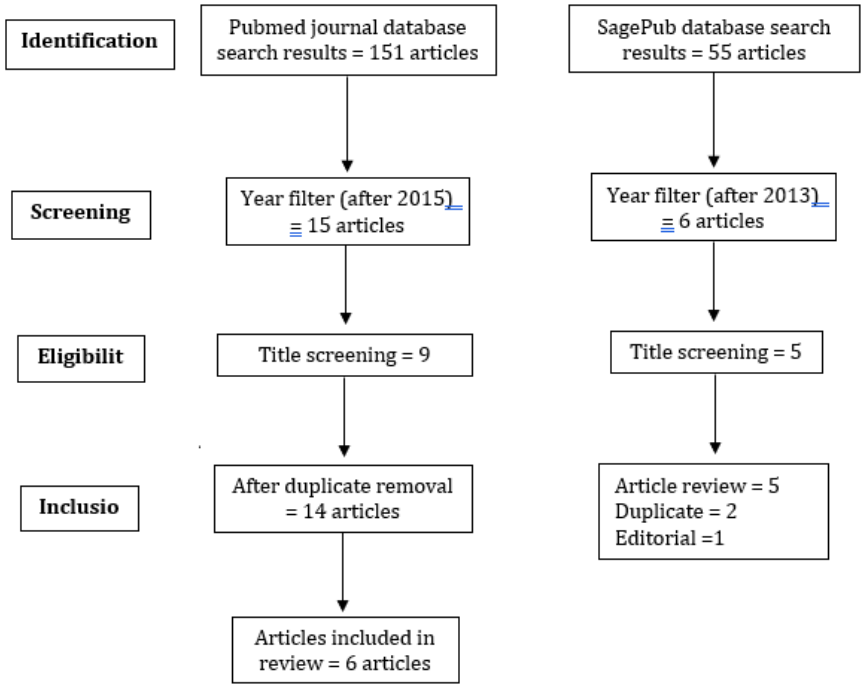

Figure 1. Article Search Flowchart

RESULT AND DISCUSSION

P. Gaibani et al. (2020) discovered that 105 out of 120 carbapenemase-producing *Enterobacteriaceae* (CPE) strains could produce KPC. Phenotypic characterization showed that most of the tested isolates (87.5%) produced *KPC*. Resistance to *ceftazidime* and *avibactam* was identified in three *KPC–K. pneumoniae* strains, which were recovered from patients with no prior exposure to these agents. Two of the three KPC-*K. pneumoniae* strains that exhibited resistance to *ceftazidime* and *avibactam* also exhibited resistance to meropenem and vaborbactam. Among the three *ceftazidime–avibactam*–resistant *KPC–K. pneumoniae* populations, two carried mutations in the *ompK36* porin associated with increased nucleotide sequences of the *blaKPC* gene. In contrast, the remaining population consisted of a mixed strain harboring the *D179Y* mutant *KPC-2*. The absence of functional *ompK35–ompK37* porins together with mutations in *ompK36* was also associated with a gradual increase in the number of *blaKPC* gene copies.

Lomovskaya et al. (2017) examined 18 *KPC–K. pneumoniae* strains exhibiting different levels of susceptibility to *meropenem* (MIC = 8–512 µg/ml) and the *meropenem–vaborbactam* combination (MIC = 0.06–32 µg/ml). Administration of *meropenem* and *vaborbactam* at 8 g/ml each reduced the frequency of resistance mutations to 1×10^{-8} in 77.8% (14/18) of the strains. The isolates were selected from a global surveillance collection that included strains with preexisting resistance mechanisms, particularly those showing MIC values at the upper range for the tested drugs. In contrast, *meropenem* at 16 g/ml was able to inhibit all examined strains. *Carbapenem*-resistant phenotypes were observed in mutants chosen at lower medication doses. Mutants derived from *OmpK36*-proficient strains showed inactivation of *ompK36* accompanied by an increased number of *blaKPC* gene copies, whereas strains exhibiting only partial *ompK36* activity displayed the opposite phenotype. Both of these traits were discovered in drug-resistant mutants that were chosen at weaker doses. No *blaKPC gene* coding-area mutations could be identified (Table 1) (Galani et al., 2019).

Table 1. The Literature Included in This Study

Author	Origin	Method	Sample Size	Result
P. Gaibani et al. (2020)	Italy	Cross-sectional	120 *carbapenemas* e-producing	Antibiotic history had no bearing on whether or not a KCP-Kp strain developed resistance to *ceftazidime*

			Enterobacteriaceae (CPE)	*and avibactam*. There is evidence that *blaKPC gene* mutations or porin deficiency contribute to reduced susceptibility to *ceftazidime/avibactam* and *meropenem/vaborbactam*.
Sun et al. (2017)	USA	Cross-sectional	18 different types of *K. pneumoniae* that produce KPC	These findings indicate that appropriate dosing of the drug combination is essential to prevent the emergence of mutant *KPC*-producing *Klebsiella pneumoniae* strains with decreased susceptibility to *meropenem–vaborbactam*. The mechanism appears to be associated with previously reported pathways involving mutations in transmembrane proteins and an increased number of *blaKPC* gene copies, rather than alterations in the *KPC* enzyme itself.
Giddins et al. (2018)	USA	Cross-sectional	8 isolates	Insertions and deletions were the most noticeable changes to this group of *CAZ-AVI* and MEM-resistant isolates' genomes. These changes were found in the collection. The rfb gene *locus* was disrupted, multiplication and translocation of *blaKPC-2* onto a new plasmid, and insertion of IS1 upstream of *ompK36*. All of these things were detected in these isolates. According to the findings of our study, *CAZ-AVI* resistance may develop in clonal situations that do not include *K. pneumoniae ST258*, in addition to other variations of *blaKPC.*
Gaibani et al., (2022)	Italy	Cross-sectional, genomic sequencing	N/I	*CAZ-AVI*, *MER-VAB*, *IMI-REL,* and CFD were all ineffective against the KPC-Kp (KPC-producing *Klebsiella pneumoniae*) BO743 strain. Strain BO743 contains one chromosome with 5,347,000 bp and three circular plasmids with 3,634,000 bp (pBO743-363Kb), 120,290 bp (pBO743-120Kb), and 54,339 bp (pBO743-54339) (pBO743-54Kb). In KPC-Kp BO743, the plasmids pBO743-54Kb and pBO743-120Kb housed *blaOXA-181* and the new *blaKPC-121*, respectively. What differentiates KPC-121 from KPC-3 is the serine insertion at position 181.

Galani et al. (2019)	Greece	Cross-sectional, Gene isolated	N/I	A clinical isolate of *KPC-23*–producing *K. pneumoniae* exhibited resistance to *ceftazidime–avibactam*, which was attributed to enhanced hydrolysis of *ceftazidime*. The absence of *OmpK35* porin almost certainly contributed to developing this resistance.
Shields et al. (2017)	USA	Cross-sectional, genomic sequencing	N/I	They showed that distinct mutations in the *blaKPC-3* gene were identified among isolates within a separate *ST258* lineage, leading to the production of altered *KPC-3* enzymes. Following site-directed gene inactivation in *K. pneumoniae*, along with plasmid transfer and cloning of *blaKPC* into competent *Escherichia coli*, the mutations were found to be resistance determinants by measuring the minimal inhibitory concentrations (MICs) of *ceftazidime-avibactam* and other drugs. It was done in order to determine whether or not the mutations were responsible for the resistance. The influence of each of the numerous KPC-3 variations on the *ceftazidime-avibactam* minimum inhibitory concentration is ranked as follows, beginning with the most significant: D179Y/T243M double substitution > D179Y > V240G.

In a study that Giddins et al. (2018) carried out, the researchers concluded that *CAZ-AVI*-resistant and MEM-resistant isolates had a diverse spectrum of genomic changes, most of which took the form of insertions and deletions. This isolation was accomplished by amplifying the *blaKPC-2* gene and then transposing it onto a new plasmid when the amplification was complete. In addition, an IS1 insertion was identified within the regulatory region preceding the *ompK36* gene, and alterations were also observed in the *rfb gene locus*. According to the results, *CAZ-AVI* resistance can develop even in clonal backgrounds that do not include *K. pneumoniae* ST258 or other *blaKPC* variants. It is the case regardless of whether or not the background contains *blaKPC*. According to Galani et al. (2019) isolates *of Klebsiella pneumoniae* were classified as multilocus sequence type ST258 and carried *blaKPC-23* as the sole carbapenemase gene in the genome.

A high degree of resistance to *imipenem* and *meropenem* was observed in the isolate, with a minimum inhibitory concentration of 512 μg/L. Resistance to *ceftazidime* was also detected, with a minimum inhibitory concentration greater than 1024 μg/L. The minimum inhibitory concentration of the ceftazidime–avibactam combination was 16 μg/L, while the minimum inhibitory concentration of *ceftazidime* alone reached 1024 μg/L. The *blaKPC-23* gene was located on a *Tn4401a* transposon inserted into a pKPQIL-type plasmid. Variations in outer membrane proteins were also identified, including a variant of *OmpK36* and a non-functional form of *OmpK35*, which have been described in earlier studies involving ST258 *Klebsiella pneumoniae* isolates. Transformation experiments using *Escherichia coli* TOP10 indicated that KPC-23 produced carbapenem minimum inhibitory concentrations comparable to those observed in KPC-2 and KPC-3.

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

KPC-23 differs from *KPC-3* by one amino acid change *(V240A)* and *KPC-2* by two amino acid modifications (V240A and H274Y). According to one research, natural variants of KPC-2 carrying the V240A and H274Y modifications showed a tenfold increase in the minimum inhibitory concentration of *ceftazidime*. This combination also enhances the ability of the enzyme to hydrolyze *ceftazidime* as well (Mehta et al., 2015). At least two years passed between the discovery of *KP-90* in Greece and the introduction of the combination antibiotic *ceftazidime-avibactam*. It is hard to gauge the extent of the problem since surveillance data showing the widespread spread of KPC-23-producing *K. pneumoniae* in Greek hospitals cannot be obtained (Galani et al., 2019).

Research involving WGS was carried out by Shields et al. (2017) showed that isolates with a different sequence type 258 sublineage developed blaKPC-3 mutations that produced mutant KPC-3 enzymes. Gene inactivation experiments conducted in *Klebsiella pneumoniae*, followed by plasmid mobilization and insertion of the *blaKPC* gene into competent *Escherichia coli,* the MICs of *ceftazidime-avibactam* and other medicines were measured, proving the changes to be resistance determinants. *KPC-3* variations are ranked according to their effect on *ceftazidime-avibactam* minimal inhibitory concentrations (MICs). D179Y > V240G because it is a double substitution (D179Y/T243M).

The changes that restored sensibility in *K. pneumoniae* isolated from two patients, the minimum inhibitory concentrations (MICs) for *meropenem* were reduced by four compared to their original values. While there was a fourfold reduction in the minimum inhibitory concentrations (MICs) of *cefepime* and *ceftriaxone* against D179Y/T243M and D179Y variant isolates, susceptibility was not re-established. The findings of the reverse transcription-PCR showed that the level of expression of *blaKPC-3* variants expressing D179Y/T243M and D179Y was lower than the baseline isolates (Livermore et al., 2015).

Discussion

From the study presented in this article, several genetic determinants appear to be involved in the development of antimicrobial resistance phenotypes. One example includes certain KPC-producing *Klebsiella pneumoniae* strains that exhibit resistance to *ceftazidime* and avibactam as a result of mutations in the *blaKPC* gene. In addition to this mechanism, other genes have also been reported to contribute to resistance. Findings reported by Giddins indicated that resistance to *ceftazidime* and avibactam may also arise from mutations occurring in the *blaKPC-2* gene, which encodes the KPC-2 enzyme, as in other variations of blaKPC (Gaibani et al., 2022; Paczosa & Mecsas, 2016). This review also indicated that *blaKPC-3* (KPC-3) contributes to reduced susceptibility to *ceftazidime* and avibactam. In addition, *blaKPC-23* (KPC-23) has been reported to exhibit resistance to *imipenem*, *meropenem*, and *ceftazidime*, which have the same MIC in inhibiting *carbapenem* with *blaKPC-2* and *blaKPC-3*. The difference between *KPC-23* and *KPC-3* is only one amino acid change, while with *KPC-2*, there are two *amino acid* changes (Galani et al., 2019).

Both naturally occurring KPC-3 mutants and site-directed mutagenesis KPC-2 mutants have been shown to have KPC mutations and are associated with resistance. In clinical isolates obtained from untreated individuals, reduced susceptibility to the combination of *ceftazidime* and avibactam has been linked to KPC overexpression as well as mutations in porin proteins (García et al., 2022). Mutations that confer resistance to *ceftazidime* and *avibactam* treatment have been found in patients, which is a significant finding. Isolates of *K. pneumoniae* generating KPC-3 or KPC-2 developed resistance to the therapy between the tenth and nineteenth day of the treatment. This resistance was linked to structural changes affecting the omega loop region of the KPC enzyme, specifically involving substitutions between R164 and D179. The rate of hydrolyzed *ceftazidime* was increasing, and *avibactam* could not prevent this process entirely because of these alterations (Tsivkovski & Lomovskaya, 2020). Furthermore, evidence suggests that alterations in porin proteins, including *OmpK35*, *OmpK36*, and *OmpK37*, in *Klebsiella pneumoniae*

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

contribute to carbapenem resistance. In addition, mutations affecting *OmpK36* have been linked to an increased copy number of the *blaKPC* gene (Lomovskaya et al., 2017).

Recently, researchers have found similar mechanisms that lead to a lower sensitivity to *ceftazidime-avibactam* susceptibility. These discoveries were made in recent times. Importantly, no alterations were detected in the coding region of the *bla*KPC gene in any of the mutants, including those originating from parental strains harboring additional resistance determinants, such as KP1096 and KP1092. Conversely, alterations in the *bla*KPC gene have been reported in patients receiving ceftazidime–avibactam therapy and in mutants exhibiting decreased susceptibility to ceftazidime–avibactam obtained from in vitro selection studies. These mutations have been linked to a decreased susceptibility to *ceftazidime-avibactam* (Clancy et al., 2013; Livermore et al., 2015; Lomovskaya et al., 2017).

This article also found an optimal dose for the *meropenem-vaborbactam* combination in KPC-*K. pneumoniae* strains with *OmpK36* mutations. However, unfortunately, Sun et al.'s study did not find mutations in the *blaKPC gene*. It was shown that varying doses of *meropenem-vaborbactam* were linked to the in vitro selection or avoidance of resistant mutants (Galani et al., 2019). When meropenem and vaborbactam were administered at 8 g/ml, most KPC-producing *K. pneumoniae* isolates were protected from the emergence of mutants exhibiting drug resistance. To prevent the selection of mutants, the concentration of meropenem was increased across every tested isolate, including two isolates that exhibited M-V MIC values of 16 and 32 µg/ml. Ensuring adequate exposure to meropenem–vaborbactam in order to suppress resistance development at infection sites is crucial for maintaining the long-term therapeutic effectiveness of this recently introduced carbapenem–lactamase inhibitor combination. The study of mutations acquired at low medication dosages revealed that most mutants had resistant phenotypes consistent with previously established *carbapenem* resistance pathways (Cannatelli et al., 2014).

Previously, research done on *oxacillinase genes* by Galani et al has revealed that *blaOXA-48* is plasmid-encoded and independent of any integron. Just upstream of the *blaOXA-48* gene is where IS1999 was found. An extra plasmid in *K. pneumoniae* 11978 included the *blaOXA-47 oxacillinase gene* within a class 1 integron. Unlike its related *β-lactamase, OXA-47* could not hydrolyze *ceftazidime* or *imipenem,* showing that its range of hydrolysis activity was somewhat restricted (OXA-1). Furthermore, the same *K. pneumoniae* isolate was shown to produce both the *β-lactamase TEM-1* and *the β-lactamase SHV-2a*. Proteins from the outer membrane showed that this isolate did not have a porin of roughly 36 kDa. Hence, this clinical isolate exhibited a substantial degree of resistance to β-lactam antibiotics, which was linked to the presence of a novel β-lactamase together with modifications in outer membrane proteins.

CONCLUSION

This systematic review identified various gene mutations and porin variations in carbapenem-resistant *K. pneumoniae*. The mutations, including *blaKPC*, *blaKPC-2*, *blaKPC-3*, and *blaKPC-23*, contribute to *carbapenem* resistance, while porin variations, such as *OmpK35*, *OmpK36*, and *OmpK37*, also play a role. An optimal combination of antibiotics should be used to address the carbapenem resistance issue. These results provide important information that may support the development of effective approaches to manage infections caused by carbapenem-resistant *K. pneumoniae*. This research discovery shows that the ideal combination of antibiotics should be custom-made for the particular strain of *K. pneumoniae* with a carbapenem-resistant genotype, particularly for KPC-K. pneumoniae strains with a change in OmpK36. This research offers imperative data for making effective strategies to battle carbapenem-resistant K. pneumoniae diseases.

SUGGESTION

Further research is recommended to clarify the clinical implications of specific blaKPC variants and porin alterations identified in this review. Multicenter genomic surveillance studies across diverse regions should be conducted in order to monitor the distribution of mutations,

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

including blaKPC-2, blaKPC-3, blaKPC-23, and changes in OmpK35, OmpK36, and OmpK37. Prospective clinical investigations are also needed to evaluate therapeutic strategies tailored to carbapenem resistant genotypes, particularly in strains carrying OmpK36 mutations associated with increased blaKPC copy numbers. In addition, pharmacodynamic studies assessing optimized dosing regimens of combinations such as *meropenem vaborbactam* and *ceftazidime avibactam* would contribute to preventing the emergence of resistant subpopulations and improving treatment outcomes.

ACKNOWLEDGMENT

The authors wish to convey their sincere gratitude to colleagues at the Clinical Microbiology Specialist Program and the Department of Microbiology, Faculty of Medicine, Universitas Indonesia, for their constructive academic discussions and methodological input during the development of this systematic review. Gratitude is also extended to the institutional library staff for their assistance in facilitating access to scientific databases, which supported the comprehensive literature search conducted in this study. The authors are thankful to the peer reviewers and editorial team whose insightful comments and recommendations contributed to improving the clarity and scientific rigor of this manuscript.

REFERENCES

Abou-assy, R. S., Aly, M. M., Amasha, R. H., Jastaniah, S., Alammari, F., & Shamrani, M. (2023). Carbapenem resistance mechanisms, carbapenemase genes dissemination, and laboratory detection methods: a review. *International Journal of Pharmaceutical Research and Allied Sciences*, *12*(1-2023), 123-138.

Alvisi, G., Curtoni, A., Fonnesu, R., Piazza, A., Signoretto, C., Piccinini, G., ... & Gaibani, P. (2025). Epidemiology and genetic traits of carbapenemase-producing enterobacterales: A global threat to human health. *Antibiotics*, *14*(2), 141. https://doi.org/10.3390/antibiotics14020141

Campos, A. C., Albiero, J., Ecker, A. B., Kuroda, C. M., Meirelles, L. E., Polato, A., ... & Teixeira, J. J. (2016). Outbreak of Klebsiella pneumoniae carbapenemase–producing K pneumoniae: A systematic review. *American Journal of Infection Control*, *44*(11), 1374-1380. https://doi.org/10.1016/j.ajic.2016.03.022

Cannatelli, A., Di Pilato, V., Giani, T., Arena, F., Ambretti, S., Gaibani, P., ... & Rossolini, G. M. (2014). In vivo evolution to colistin resistance by PmrB sensor kinase mutation in KPC-producing Klebsiella pneumoniae is associated with low-dosage colistin treatment. *Antimicrobial agents and chemotherapy*, *58*(8), 4399-4403. https://doi.org/10.1128/aac.02555-14

Castanheira, M., Simner, P. J., & Bradford, P. A. (2021). Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection. *JAC-antimicrobial resistance*, *3*(3), dlab092. https://doi.org/10.1093/jacamr/dlab092

Clancy, C. J., Chen, L., Hong, J. H., Cheng, S., Hao, B., Shields, R. K., ... & Nguyen, M. H. (2013). Mutations of the ompK36 porin gene and promoter impact responses of sequence type 258, KPC-2-producing Klebsiella pneumoniae strains to doripenem and doripenem-colistin. *Antimicrobial agents and chemotherapy*, *57*(11), 5258-5265. https://doi.org/10.1128/aac.01069-13

Du, Y., Mu, S., Liu, Y., Yuan, Y., Zhu, Y., Ma, L., ... & Wang, S. (2022). The genomic characterization of KPC-producing Klebsiella pneumoniae from the ICU of a Teaching Hospital in Shanghai, China. *Infection and Drug Resistance*, 69-81. https://doi.org/10.2147/IDR.S343673

Falagas, M. E., Asimotou, C. M., Zidrou, M., Kontogiannis, D. S., & Filippou, C. (2025). Global epidemiology and antimicrobial resistance of Klebsiella pneumoniae carbapenemase

(KPC)-producing Gram-negative clinical isolates: a review. *Microorganisms*, *13*(7), 1697. https://doi.org/10.3390/microorganisms13071697

Follador, R., Heinz, E., Wyres, K. L., Ellington, M. J., Kowarik, M., Holt, K. E., & Thomson, N. R. (2016). The diversity of Klebsiella pneumoniae surface polysaccharides. *Microbial genomics*, *2*(8), e000073. https://doi.org/10.1099/mgen.0.000073

Gaibani, P., Amadesi, S., Lazzarotto, T., & Ambretti, S. (2022). Genome characterization of a Klebsiella pneumoniae co-producing OXA-181 and KPC-121 resistant to ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam and cefiderocol isolated from a critically ill patient. *Journal of Global Antimicrobial Resistance*, *30*, 262-264. https://doi.org/10.1016/j.jgar.2022.06.021

Gaibani, P., Re, M. C., Campoli, C., Viale, P. L., & Ambretti, S. (2020). Bloodstream infection caused by KPC-producing Klebsiella pneumoniae resistant to ceftazidime/avibactam: epidemiology and genomic characterization. *Clinical Microbiology and Infection*, *26*(4), 516-e1. https://doi.org/10.1016/j.cmi.2019.11.011

Galani, I., Antoniadou, A., Karaiskos, I., Kontopoulou, K., Giamarellou, H., & Souli, M. (2019). Genomic characterization of a KPC-23-producing Klebsiella pneumoniae ST258 clinical isolate resistant to ceftazidime-avibactam. *Clinical Microbiology and Infection*, *25*(6), 763-e5. https://doi.org/10.1016/j.cmi.2019.03.011

García, P., Brito, B., Alcalde-Rico, M., Munita, J. M., Martínez, J. R., Olivares-Pacheco, J., ... & Wozniak, A. (2022). Acquisition of resistance to ceftazidime-avibactam during infection treatment in Pseudomonas aeruginosa through D179Y mutation in one of two blaKPC-2 gene copies without losing carbapenem resistance. *Frontiers in Cellular and Infection Microbiology*, *12*, 981792. https://doi.org/10.3389/fcimb.2022.981792

Giddins, M. J., Macesic, N., Annavajhala, M. K., Stump, S., Khan, S., McConville, T. H., ... & Uhlemann, A. C. (2018). Successive emergence of ceftazidime-avibactam resistance through distinct genomic adaptations in bla KPC-2-harboring Klebsiella pneumoniae sequence type 307 isolates. *Antimicrobial agents and chemotherapy*, *62*(3), 10-1128. https://doi.org/10.1128/aac.02101-17

Hobson, C. A., Pierrat, G., Tenaillon, O., Bonacorsi, S., Bercot, B., Jaouen, E., ... & Birgy, A. (2022). Klebsiella pneumoniae carbapenemase variants resistant to ceftazidime-avibactam: an evolutionary overview. *Antimicrobial agents and chemotherapy*, *66*(9), e00447-22. https://doi.org/10.1128/aac.00447-22

Hu, Y., Anes, J., Devineau, S., & Fanning, S. (2021). Klebsiella pneumoniae: prevalence, reservoirs, antimicrobial resistance, pathogenicity, and infection: a hitherto unrecognized zoonotic bacterium. *Foodborne pathogens and disease*, *18*(2), 63-84. https://doi.org/10.1089/fpd.2020.284

Jelic, M., Butic, I., Plecko, V., Cipris, I., Jajic, I., Bejuk, D., ... & Andrasevic, A. T. (2016). KPC-producing Klebsiella pneumoniae isolates in Croatia: a nationwide survey. *Microbial drug resistance*, *22*(8), 662-667. https://doi.org/10.1089/mdr.2015.0150

Jin, X., Chen, Q., Shen, F., Jiang, Y., Wu, X., Hua, X., ... & Yu, Y. (2021). Resistance evolution of hypervirulent carbapenem-resistant Klebsiella pneumoniae ST11 during treatment with tigecycline and polymyxin. *Emerging microbes & infections*, *10*(1), 1129-1136. https://doi.org/10.1080/22221751.2021.1937327

Karampatakis, T., Tsergouli, K., & Behzadi, P. (2023). Carbapenem-resistant Klebsiella pneumoniae: virulence factors, molecular epidemiology and latest updates in treatment options. *Antibiotics*, *12*(2), 234. https://doi.org/10.3390/antibiotics12020234

Ke, Y., Zeng, Z., Liu, J., & Ye, C. (2025). Capsular polysaccharide as a potential target in hypervirulent and drug-resistant Klebsiella pneumoniae treatment. *Infection and Drug*

Resistance, 1253-1262. https://doi.org/10.2147/IDR.S493635

Ko, K. S. (2017). The contribution of capsule polysaccharide genes to virulence of Klebsiella pneumoniae. *Virulence*, *8*(5), 485-486. https://doi.org/10.1080/21505594.2016.1240862

Lee, C. R., Lee, J. H., Park, K. S., Kim, Y. B., Jeong, B. C., & Lee, S. H. (2016). Global dissemination of carbapenemase-producing Klebsiella pneumoniae: epidemiology, genetic context, treatment options, and detection methods. *Frontiers in microbiology*, *7*, 895. https://doi.org/10.3389/fmicb.2016.00895

Li, B., Zhao, Y., Liu, C., Chen, Z., & Zhou, D. (2014). Molecular pathogenesis of Klebsiella pneumoniae. *Future microbiology*, *9*(9), 1071-1081. https://doi.org/10.2217/fmb.14.48

Livermore, D. M., Warner, M., Jamrozy, D., Mushtaq, S., Nichols, W. W., Mustafa, N., & Woodford, N. (2015). In vitro selection of ceftazidime-avibactam resistance in Enterobacteriaceae with KPC-3 carbapenemase. *Antimicrobial agents and chemotherapy*, *59*(9), 5324-5330.

Lomovskaya, O., Sun, D., Rubio-Aparicio, D., Nelson, K., Tsivkovski, R., Griffith, D. C., & Dudley, M. N. (2017). Vaborbactam: spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in Enterobacteriaceae. *Antimicrobial agents and chemotherapy*, *61*(11), 10-1128. https://doi.org/10.1128/aac.01443-17

Luo, M., Yang, X. X., Tan, B., Zhou, X. P., Xia, H. M., Xue, J., ... & Li, Y. L. (2016). Distribution of common pathogens in patients with pyogenic liver abscess in China: a meta-analysis. *European Journal of Clinical Microbiology & Infectious Diseases*, *35*(10), 1557-1565. https://doi.org/10.1007/s10096-016-2712-y

Martin, R. M., & Bachman, M. A. (2018). Colonization, infection, and the accessory genome of Klebsiella pneumoniae. *Frontiers in cellular and infection microbiology*, *8*, 4. https://doi.org/10.3389/fcimb.2018.00004

Mehta, S. C., Rice, K., & Palzkill, T. (2015). Natural variants of the KPC-2 carbapenemase have evolved increased catalytic efficiency for ceftazidime hydrolysis at the cost of enzyme stability. *PLoS pathogens*, *11*(6), e1004949. https://doi.org/10.1371/journal.ppat.1004949

Mohammadpour, D., Memar, M. Y., Leylabadlo, H. E., Ghotaslou, A., & Ghotaslou, R. (2025). Carbapenem-Resistant Klebsiella pneumoniae: A comprehensive review of phenotypic and genotypic methods for detection. *The Microbe*, *6*, 100246. https://doi.org/10.1016/j.microb.2025.100246

Mohd Asri, N. A., Ahmad, S., Mohamud, R., Mohd Hanafi, N., Mohd Zaidi, N. F., Irekeola, A. A., ... & Yusof, N. Y. (2021). Global prevalence of nosocomial multidrug-resistant Klebsiella pneumoniae: a systematic review and meta-analysis. *Antibiotics*, *10*(12), 1508. https://doi.org/10.3390/antibiotics10121508

Munoz-Price, L. S., Poirel, L., Bonomo, R. A., Schwaber, M. J., Daikos, G. L., Cormican, M., ... & Quinn, J. P. (2013). Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. *The Lancet infectious diseases*, *13*(9), 785-796.

Paczosa, M. K., & Mecsas, J. (2016). Klebsiella pneumoniae: going on the offense with a strong defense. *Microbiology and molecular biology reviews*, *80*(3), 629-661. https://doi.org/10.1128/mmbr.00078-15

Piper, B. J., Alinea, A. A., Wroblewski, J. R., Graham, S. M., Chung, D. Y., McCutcheon, L. R., ... & Bordonaro, M. (2019). A quantitative and narrative evaluation of Goodman and Gilman's Pharmacological Basis of Therapeutics. *Pharmacy*, *8*(1), 1. https://doi.org/10.3390/pharmacy8010001

Pitout, J. D., Nordmann, P., & Poirel, L. (2015). Carbapenemase-producing Klebsiella pneumoniae, a key pathogen set for global nosocomial dominance. *Antimicrobial agents and chemotherapy*, *59*(10), 5873-5884. https://doi.org/10.1128/aac.01019-15

Rendueles, O. (2020). Deciphering the role of the capsule of Klebsiella pneumoniae during pathogenesis: A cautionary tale. *Molecular microbiology*, *113*(5), 883-888. https://doi.org/10.1111/mmi.14474Digital Object Identifier (DOI)

Reyes, J., Aguilar, A. C., & Caicedo, A. (2019). Carbapenem-resistant Klebsiella pneumoniae: microbiology key points for clinical practice. *International journal of general medicine*, 437-446. https://doi.org/10.2147/IJGM.S214305

Sahly, H., Podschun, R., & Ullmann, U. (2002). Klebsiella infections in the immunocompromised host. *The biology and pathology of innate immunity mechanisms*, 237-249. https://doi.org/10.1007/0-306-46831-X_21

Santino, I., Bono, S., Nuccitelli, A., Martinelli, D., Petrucci, C., & Alari, A. (2013). Microbiological and molecular characterization of extreme drug-resistant carbapenemase-producing Klebsiella pneumoniae isolates. *International Journal of Immunopathology and Pharmacology*, *26*(3), 785-790. https://doi.org/10.1177/039463201302600325

Satlin, M. J., Chen, L., Patel, G., Gomez-Simmonds, A., Weston, G., Kim, A. C., ... & Kreiswirth, B. N. (2017). Multicenter clinical and molecular epidemiological analysis of bacteremia due to carbapenem-resistant Enterobacteriaceae (CRE) in the CRE epicenter of the United States. *Antimicrobial agents and chemotherapy*, *61*(4), 10-1128. https://doi.org/10.1128/aac.02349-16

Shields, R. K., Chen, L., Cheng, S., Chavda, K. D., Press, E. G., Snyder, A., ... & Clancy, C. J. (2017). Emergence of ceftazidime-avibactam resistance due to plasmid-borne bla KPC-3 mutations during treatment of carbapenem-resistant Klebsiella pneumoniae infections. *Antimicrobial agents and chemotherapy*, *61*(3), 10-1128. https://doi.org/10.1128/aac.02097-16

Songsantiphap, C., Vanichanan, J., Chatsuwan, T., Asawanonda, P., & Boontaveeyuwat, E. (2022). Methylene blue–mediated antimicrobial photodynamic therapy against clinical isolates of extensively drug resistant gram-negative Bacteria causing nosocomial infections in Thailand, an in vitro study. *Frontiers in cellular and infection microbiology*, *12*, 929242. https://doi.org/10.3389/fcimb.2022.929242

Sun, D., Rubio-Aparicio, D., Nelson, K., Dudley, M. N., & Lomovskaya, O. (2017). Meropenem-vaborbactam resistance selection, resistance prevention, and molecular mechanisms in mutants of KPC-producing Klebsiella pneumoniae. *Antimicrobial agents and chemotherapy*, *61*(12), 10-1128. https://doi.org/10.1128/aac.01694-17

Tsai, C. C., Lin, J. C., Chen, P. C., Liu, E. Y. M., Tsai, Y. K., Yu, C. P., ... & Siu, L. K. (2023). A 20-year study of capsular polysaccharide seroepidemiology, susceptibility profiles, and virulence determinants of Klebsiella pneumoniae from bacteremia patients in Taiwan. *Microbiology Spectrum*, *11*(3), e00359-23. https://doi.org/10.1128/spectrum.00359-23

Tsivkovski, R., & Lomovskaya, O. (2020). Potency of vaborbactam is less affected than that of avibactam in strains producing KPC-2 mutations that confer resistance to ceftazidime-avibactam. *Antimicrobial agents and chemotherapy*, *64*(4), 10-1128. https://doi.org/10.1128/aac.01936-19

Tzouvelekis, L. S., Markogiannakis, A., Psichogiou, M., Tassios, P. T., & Daikos, G. L. (2012). Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clinical microbiology reviews*, *25*(4), 682-707. https://doi.org/10.1128/cmr.05035-11

