International Journal of General Medicine

Dovepress
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REVIEW

# Carbapenem-Resistant *Klebsiella pneumoniae*: Microbiology Key Points for Clinical Practice

This article was published in the following Dove Press journal:
*International Journal of General Medicine*

Jorge Reyes[1,2]
Ana Cristina Aguilar[1,3]
Andrés Caicedo[1,3,4]

[1]Colegio de Ciencias Biológicas y Ambientales, Instituto de Microbiología, Universidad San Francisco de Quito (USFQ), Quito 17-09-01, Ecuador; [2]Facultad de Ciencias Químicas, Universidad Central del Ecuador, Quito, Ecuador; [3]Colegio de Ciencias de la Salud (COCSA), Escuela de Medicina, Universidad San Francisco de Quito (USFQ), Quito 17-12-841, Ecuador; [4]Sistemas Médicos (SIME), Universidad San Francisco de Quito (USFQ), Quito 17-12-841, Ecuador



**Abstract:** Carbapenemase–producing *Klebsiella pneumoniae* strains (Cp-Kpn) represent a challenge for clinical practitioners due to their increasing prevalence in hospital settings and antibiotic resistance. Clinical practitioners are often overwhelmed by the extensive list of publications regarding Cp-Kpn infections, treatment, characteristics, identification, and diagnosis. In this perspective article, we provide key points for clinical practitioners to consider for improved patient management including identification of risk factors and strategies for treatment. Additionally, we also discuss genetic underpinnings of antibiotic resistance, implementation of an antimicrobial stewardship program (ASP), and use of automated systems for detection of Cp-Kpn. Collectively, implementation of such key points would enhance clinical practices through providing practical knowledge to health professionals worldwide.

**Keywords:** carbapenemase–producing *Klebsiella pneumonia*, clinical practitioners, management

## Introduction

*K. pneumoniae*, described by Edwin Klebs in 1875, is a gram-negative bacterium belonging to the *Enterobacteriaceae* family. This microorganism is part of the healthy microbiome of individuals and colonizes many parts of the body. Despite its role as a healthy component of the microbiome, it can cause severe infections in critically ill patients, newborns, immunocompromised individuals or those with other risk factors in healthcare establishments. Antibiotics such carbapenems are widely used to treat infections, especially those caused by *Enterobacteriaceae*, a producer of extended-spectrum β-lactamase (ESBL); however, the use or misuse of such antibiotics has contributed to the appearance of isolates resistant to carbapenems.[1]

Carbapanem-resistant *K. pneumoniae* (Cr-KPN) is a pathogen that affects people worldwide, with prevalence in low, middle and upper income countries. Resistance to carbapenem is mediated by two primary mechanisms. First, Cr-KPN is able to produce β-lactamases with the ability to hydrolyze cephalosporins such *AmpC* cephalosporinase e.g. DHA-1 and CMY-2 or ESBL e.g. CTX-M-2 in combination with decreased membrane permeability in the cell wall.[2,3] The second mechanism is mediated by the production of a β-lactamases capable of hydrolyzing most β-lactams antibiotics including carbapenems. According the Ambler classification it belongs to class A (*K. pneumoniae* carbapenemase, KPC), class B or metallo-β-lactamases (MBL) (New Delhi metallo-β-lactamases, NDM) and class D (OXA-48-like

Correspondence: Jorge Reyes
Instituto de Microbiología, Universidad San Francisco de Quito (USFQ), Diego de Robles y Pampite S/N, Quito 17-09-01, Ecuador
Tel +593 98 44 9 00 22
Email jorgereyes83@gmail.com

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DovePress
http://doi.org/10.2147/IJGM.S214305

carbapenemases).[4] The NDM carbapenemase was reported from *K. pneumoniae* and *Escherichia coli* in 2009, similar to other member of MBL it requires of zinc for hydrolysis of β-lactam antibiotics and their activity could be inhibited by ethylenediaminetetraacetic acid (EDTA) as chelating agent.[5] KPC–producer *K. pneumoniae* (KPC-Kp) is a pathogen with a high capacity for clonal expansion and exchange of mobile genetic elements (MGEs) promoting increased resistance. KPC-Kp among their capacities to generate resistance can also persist in human reservoirs and create biofilms, which provide protection from hospital disinfection protocols.[6]

Since the first report of KPN-Kp in the United States in 1996,[7] its presence has been evidenced in many other countries including China, Italy,[8] Brasil, Venezuela, Colombia, Ecuador and Argentina.[9] In these countries, KPC-Kp infections have contributed to an increased mortality and substantial costs for health care systems. Detection of KPC-Kp is carried out in clinical microbiology laboratories (CMLs) and is the first step in that physicians take when determining a therapeutic strategy (dose and time of administration) involving active antibiotics; however, accurate and consistent interpretation of CML reports is a long-standing problem across health care systems, particularly in low and middle income countries. Clinical practitioners without appropriate training or CMLs removed from medical facilities contributed to the erroneous therapeutic decision-making that facilitates the spread of antibiotic resistance, which ultimately results in adverse outcomes for patients.

The vast existing literature detailing KPC-Kp, its pathogenicity, mechanisms of antibiotic resistance and assays used for its detection in CMLs has not been clearly outlined for physicians in clinical practice. The aim of this perspective article is to provide key points of information for students and clinical practitioners (non-laboratory related) about infections characteristics and CML reports regarding KPC-Kp. By increasing practitioners' understanding and interpretation of CML reports and clinical facilities, such clear, evidence-based information will enhance therapeutic strategies and patient outcomes.

## Risk Factors and Strategies for Treating Carbapenemase-Producing *Klebsiella pneumoniae* (Cp-Kpn) Infections

Nosocomial dissemination of Cp-Kpn results primarily from failure to properly disinfect surfaces and medical equipment. Environments routinely exposed to water and humidity, such as drains, sinks, faucets, and other locations where liquids are dispensed, are places were pathogens like Cp-Kpn can survive and disseminate, thus increasing the risk of bacterial outbreaks.[10,11] Medical equipment and devices are also common vectors of Cp-Kpn in hospitals.[12] It has been reported that Cp-Kpn can colonize medical equipment such as duodenoscopes and be transmitted to other patients.[13] Healthcare professionals' uniforms and protective clothing such as gown and gloves can also become contaminated with Cp-Kpn after patient examination if not properly used or discarded.[14] The reinforcement of hygiene protocols in healthcare facilities appears to be the most important measure for preventing outbreaks as no direct associations have been found between prevalence of Cp-Kpn outbreaks and differences in institutional infrastructure in low versus high-income countries.[8]

In recent years, reports of Cp-Kpn outbreaks, particularly KPC-Kp, have increased worldwide due to the lack of appropriate medical intervention, prolongated hospitalization, presence of comorbidities, and overuse of antibiotics, among other factors.[6] Healthcare-acquired infections are a common and major concern across hospital settings in Greece, the USA, Israel, Spain, China, Colombia, Brazil, and Italy (Xu et al, 2017). Mortality rates among patients infected by Cp-Kpn is approximately 40–50%.[15,16] Prior use of fluoroquinolones, carbapenems or cephalosporins antibiotics, long-term intensive care, chronic renal failure, high APACHE III score and, more recently, the emergency of Cp-Kpn colistin-resistant isolates have all been found to contribute to poor patient outcomes.[17,18]

The Centers for Disease Control and Prevention (CDC) has released guidelines for controlling the spread of carbapenem-resistant *Enterobacteriaceae* in healthcare facilities based on the following key points: 1) education and training for healthcare professionals and supportive personnel to reinforce protocols of hand hygiene, 2) patient contact precautions, 3) minimal use of invasive devices, and 4) environmental cleaning. Active surveillance and continuous testing for quality hospital standards are recommended. Early laboratory identification and notification of bacteria strains is also emphasized as key for prescription and timely antibiotic therapy. Additionally, the implementation of an antimicrobial stewardship program is suggested as this will provide support in the fast identification of colonization or infected status of a patient.[19] In support of this evidence, empirical treatment based on risk factors and prompt decision-making has been shown to help reduce mortality

related to Cp-Kpn infections in healthcare institutions.[20,21] Direct communication between CMLs and clinicians facilitates rapid diagnosis in these settings, which leads to faster adoption of targeted therapeutic strategies and effective combination of antibiotics, ultimately improving patient outcomes, especially among critically ill patients.[22]

## Antibiotic Resistance and Genetic Basis of *bla*$_{KPC}$

The antibiotics imipenem, meropenem, ertapenem, and doripenem are members of the β-lactam family, and most frequently used to treat *Enterobacteriaceae* infections, especially in ESBLs-producing strains. The efficacy of these antibiotics comes from their possession of a reactive β-ring, similar to that of penicillin, cephalosporin and monobactam. Their trans configuration at the C-5–C-6 bond gives these antibiotics increased potency and the capability to inhibit cell wall synthesis by preventing cross-linking of peptidoglycan and transpeptidases (Papp-Wallace, Endimiani, Taracila, & Bonomo, 2011).

The mechanisms of carbapenem resistance in *K. pneumoniae* and other *Enterobacteriaceae* strains depend on β-lactamases production, such as ESBLs. ESBLs are encoded in plasmids or by hyperproduction of chromosomally-encoded AmpC cephalosporinases (AmpC) together with the presence of porin alterations in the bacterial wall delaying the diffusion of antibiotics into the bacterial cell; however, the production of enzymes with carbapenemase activity hydrolyzing β-lactam antibiotics seems the most common mechanism of antibiotic resistance.[23] For example, the enzymes KPC, BKC and SME carbapenemase, which all fall under the category of Class A β-lactamases, contain serine residues in their active site that hydrolyze β-lactam antibiotics.[24–26] The presence of KPC carbapenemase in *K. pneumoniae* and different *Enterobacteriaceae* species isolates, depends, in part, upon whether or not it is located on a mobile genetic element (MGE), such as conjugative plasmids e.g. IncFII, IncL/M, IncA/C,[27] and its proximity to Tn*4401* transposons[28] or non-Tn*4401* elements (NTE-KPC).[29] The presence of plasmid-self transmitting pKpQIL (group incFII plasmid) harboring *bla*$_{KPC}$ in *K. pneumoniae* complex clonal (CC)258 (an international clone), has been reported to increase bacterial fitness by providing an advantage over isolates harboring different plasmids. Targeting sources of resistance like those found in pKpQIL would decrease the likelihood of bacterial dissemination in nosocomial settings.[30]

## The Role of Clinical Microbiology in Antimicrobial Stewardship Programs (ASPs) in Order to Effectively Control KPC-Kp

As previously described, the spread of KPC-Kp is an important concern across health care systems in both developed and emerging countries.[4] Implementation of hospital-based ASPs that emphasize the optimization of antibiotic use for controlling multidrug resistant bacteria (MDR) infections and preventing new resistance are needed in order to address increasing bacterial resistance in hospital settings. An ASP program should promote effective antibiotic treatment that avoids use of unnecessary antibiotics, basing its practice on de-escalation therapy and evidence-based guidelines to overcome empirical therapeutic errors and adverse events (*Clostridium difficile* infections).[31] To optimize the benefits of an ASP in a hospital setting, active participation of clinical microbiologists is a necessary component of multidisciplinary teams of health professionals. Close collaboration between clinical microbiologists, ID physicians, and clinical practitioners would facilitate the exchange of information, recognition of unusual mechanisms of resistance in pathogens, the application of accurate antimicrobial testing assays, swift communication, and early therapeutic intervention.[19]

In CML the phenotypic tests to detect carbapenemase production in *Enterobacteriaceae* are widely used specially in low incoming countries, in some cases the reagents availability and low costs are the main factors implicated in their use. Thus, in isolates with carbapenemase production suspected the use of tests based in inhibitors such boronic acid compounds or EDTA to detect KPC or MBL carbapenemases respectively has become widespread in these laboratories.[32] Recently, the modified carbapenem inactivation method (mCIM) has replaced to modified Hodge test (MHT) in CML due its greater capacity to detect the carbapenemase activity in isolates carbapenem resistant, is easy to perform and their low costs. The use of colorimetric assays such Carba NP or related is a common practice to detect carbapenemases from isolates or blood culture bottles, however, the costs could be a limitation for routine use.[33] In the practice, the phenotypic tests are recommended only for epidemiological or infection control, however the misinterpretation of the results and time of effort without a congruent diagnose (strain identification, resistance and state of patient) could interfere with therapeutic decision-making.

New laboratory tests have been reported to provide information about the detection and analysis specially of KPC carbapenemases production, changing the ways in which hospitals prevent the spread of pathogens. Control of Cp-Kpn infections inside the hospital and communication about their management, particularly in the spread of KPC-Kp, pose a challenge in part because laboratory reports are not easily understood by infectious disease (ID) physicians and clinical practitioners.[34]

## The Use of Automated Systems for Detection of KPC Carbapenemase

In CMLs, antibiotic susceptibility testing (AST) can be performed by using a broth dilution test (BD), antimicrobial gradient method (AG), or disk diffusion test (DD), which determines Minimum Inhibitory Concentration (MIC) values through of BD and AG methodologies.[35] Protocols for interpreting these tests are based upon breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST). This breakpoint allows for greater detection of the number of carbapenemase -producer *Enterobacteriaceae* isolates; however, some of these strains could be classified as carbapenem sensitive, especially if using Meropenem. The level of MIC may depend upon its association with different mechanisms (e.g. other β-lactamases enzymes or the presence of porins).[36] For this reason, MIC determination must be fast, accurate, and show the full range of MIC values for any antibiotic, especially before the administration of treatment. The Food and Drug Administration (FDA) of the United States has approved several AST automated assays, and they are currently being employed in several reference CMLs. Automation of AST has brought several advantages, including rapid generation of susceptibility test results (3.5–16 h), fewer sample manipulations, and increased accuracy in species identification and of results overall.[37]

Each automatized assay has advantages and disadvantages in the determination and interpretation of MIC values, and shortcomings must be managed carefully when detecting and reporting the mechanisms of antibiotic resistance. The Vitek 2 system, produced by bioMérieux, analyzes several microliters of a given antibiotic after it has been poured into plastic cards. Assays are monitored for turbidity and subsequently interpreted by an Advanced Expert System (AES). Another automatized assay, the Phoenix system (BD Diagnostic Systems) utilizes the BDXpert system, a rule-based software that is capable of interpreting and give recommendations related to the organism identified by broth microdilution results based in CLIS and EUCAST documents reports. In addition, the assay system includes EpiCenter software, which conducts epidemiological analyses for monitoring multidrug resistant bacteria in hospital settings.[38] The MicroScan assay (Beckman Coulter) is powered by LabPro AlertEX System software and detects atypical results in panels. The Sensititre (Thermo Scientific™) consists of plates with antibiotic dilutions powered by the ARIS™ 2X System and provides automatic, non-extrapolated reads of the MIC values, simultaneously reducing the workload for lab technicians and improving the accuracy of results. Despite each method's unique advantages, utilizing different automated platforms for detecting carbapenem resistance in *K. pneumoniae* harboring $bla_{KPC}$ can lead to discrepancies across studies, which results in frequent reporting of very major errors (VME). VME of true-resistant isolates has led to cases of failure in antibiotic therapy. For example, Tenover et al showed discrepant results for imipenem and meropenem determination in 15 *bla*KPC-positive *K. pneumonia*. After being characterized by isoelectric focusing, all strains were found to be resistant or intermediate to imipenem and meropenem using broth microdilution (BMD) as a gold standard. VME were observed in imipenem determinations, MicroScan: 1 (6.7%) Phoenix: 2 (13.3%), Vitek: 10 (67%), Vitek2: 5 (33%) isolates. Sensititre showed 13 (87%) strains sensitive to imipenem, and 12 (80%) to meropenem.[39] Bratu et al showed similar results of VME when testing resistance to imipenem in $bla_{KPC}$-positive *Klebsiella pneumonia* after conducting analyses using the Vitek system (1 isolate) and MicroScan (2 isolates).[40]

To reduce VME, breakpoint updates for carbapenem and other antibiotics were established in 2010 by the CLSI. This modification decreased the occurrence of errors, and several studies have reported a subsequent increase in specificity. Doern et al showed that the updated CLSI breakpoints resulted in better detection of KPC-producing *K. pneumoniae* and KPC-producing non-*K. pneumoniae*.[41] Their results were corroborated by Woodford et al in their study assessing three commercial systems to detect carbapenem resistant isolates, which showed that the sensitivity and specificity values for the presence of carbapenemase were 100%/0% to BD Phoenix, 82 to 85%/6 to 19% in MicroScan, and 74%/38% to Vitek 2. No VMEs were reported in KPC-producing *Enterobacteriaceae*.[42] Pasteran et al, proposed the importance of simultaneously testing two

or more carbapenems (impenem and meropenem) in Vitek 2 systems in order to enhance the detection of carbapenemase production in *Enterobacteriacea*e, including those KPC-producing strains.[43]

Phenotypic tests for the detection of AmpC inhibition would result helpful in the distinction of AmpC β-lactamases from ESBL and Metallo-β-lactamases (MBL). Tests like the AmpC disk, Gots (Modified Hodge Test, MHT) and three-dimentional test allow its detection when no molecular analysis are available. Important to point out, MHT can provide false negative information about AmpC and EMBL active bacteria being positive for the AmpC Disk Test. The Disk Test would be helping to permeabilize gram-negative cells β-lactamases release. AmpC β-lactamases and MBL can be detected by multiplex AmpC PCR with high consistency.[44,45]

During CML analysis, AST can present several challenges that should be carefully considered as they have the potential to influence results. The inoculum effect, the algorithm used to detect carbapenem resistance, and the type of card used to identify the resistance can influence MIC determination.[46] For example, in clinical practice, the fixed and specific range of antibiotic dilutions incorporated in different panels in the automatized assays make it difficult to know whether the MIC values of meropenem or imipenem are out of range; however, customizing cards by incorporating specific antibiotics and their dilution concentrations has enabled microbiologists to overcome this problem. The resulting MIC values are very important in decision-making regarding therapeutic management of infections by KPC-Kp. This topic has been highlighted by Tumbarello, who showed a low mortality rate in bloodstream infections using meropenem in antibiotic schemes, especially in strains with ≤ 8 mg/L.[18] In their study, Del Bono et al used the values of pharmacokinetic/pharmacodynamic (PK/PD) targets of meropenem (MEM). These values were not reached in critically-ill patients with bloodstream infections (BSI) due to isolates of KPC-Kp with MEM minimum inhibitory concentrations (MICs) ≥16 mg/L.[47] Additionally, a practical alternative for improving the identification of KPC-Kp could be to perform gradient diffusion methods or customized cards. In summary, the clinical practitioner must know and understand the presence of the VME issues specific to each automatized assay used in the CML, the necessity of testing two or more carbapenems in order to detect resistance, how to interpret the MIC, and how to make appropriate decisions regarding the therapeutic strategy.

## Molecular Methods and the Detection of KPC Carbapenemase for Therapeutic Decision-Making

In ASP, quick generation of an AST report is crucial for accurately prescribing antibiotic therapy, especially for patients with sepsis. Despite the advances of automation in CML analysis, DD, BD and AG testing methods all require considerable time (24–48 hrs) to yield results. Performing such assays requires a pure culture of a given pathogen and time to grow and estimate their susceptibility. Several new technologies that draw upon molecular methodologies have been introduced in CMLs in order to overcome the challenges related to time-intensive testing. For example, the molecular antibiogram (MA) is an alternative tool that detects resistance mechanisms clinically relevant to predicting clinical resistance by hydrolysis of antibiotics.[48] Several panel-based molecular diagnoses for MA, approved by the FDA, detect pathogens from samples such as blood culture bottles, respiratory secretions, stool, and cerebrospinal fluid. In cases of sepsis, the FilmArray Blood Culture Identification (BCID) panel (BioFire Diagnostics, LLC) and Verigene Gram-positive blood culture (BC-GP) and Gram-negative blood culture (BC-GN) tests (Luminex Corporation) can identify a wide range of pathogens and include the detection of *mecA, VanA, VanB,* $bla_{KPC}$, $bla_{NDM}$, $bla_{OXA}$, $bla_{IMP}$ and $bla_{CTX-M}$ genes, all related to MRS, directly from blood-cultured bottles.[49]

Several published studies showed clinical and therapeutic advantages for the use of MA in the identification of pathogens and the presence of the most common resistance genes. MA testing panels for Gram-positive and Gram-negative bacteria provide fast CML reports, helping physicians to effectively elect courses of treatment. Nevertheless, increasing the quantity of studies regarding the MA testing panels for KPC-Kp is important for continuing its application in multiple clinical settings. Despite its costliness, the application of MA has been found to decrease mortality rates, the time to de-escalation of antibiotics, and unnecessary antibiotic initiation. ASP has been shown to decrease 1) infections by resistant organisms such as vancomycin resistant enterococci (VRE), 2) patients length of stay (LOS), and 3) costs related to health care.[50–55] As with any other molecular test, the potential for contamination of sample bottles by commensal bacteria could generate uncertainty when clinicians make decisions regarding treatment. To apply MA testing, a protocol with quality-control standards must be implemented for the handling of samples and

conducting procedures in order to detect the highest number of pathogens possible and to rule out the possibility of contamination by previous Gram stains. Though ASP has been shown to improve patient mortality rates in cases of sepsis related to KPC-Kp, more evidence of its clinical and therapeutic impact is needed, particularly in hospital settings of low and middle-income countries.

The sensitivity and specificity of molecular assays for detecting $bla_{KPC}$ genes from blood cultures are approximately 100% and 98%, respectively.[56–58] Hill et al evaluated the accuracy of Verigene in Gram-Negative Blood Culture (BC-GN) (Nanosphere, Inc., Northfield, IL) In 54 samples tested, 51 isolates resulted correctly identified and the overall results showed that 31% of the patients could have been identified 33 hrs sooner and thus could have received earlier.[59] Neuner et al included 877 patients, of which 6 patients were identified as possessing the $bla_{KPC}$ gene by employing the Verigene assay. Overall, these results show that the application of ASP combined with MA decreased the time of antimicrobial switch, active therapy administration, and LOS.[60]

Despite evidence of MA's potential to improve clinical and therapeutic results in cases of antibiotic resistant bacteria, MA diagnosis related to $bla_{KPC}$ determination is not sufficient, and important factors related to its limitations should be taken in consideration. Even if MA could be applied in blood samples, MIC determination is also necessary in order to apply an optimal antibiotic combination. The expression of $bla_{KPC}$ in *K. pneumoniae* is not uniform and could stem from DNA regulatory changes upstream of $bla_{KPC}$ gene, possibly affecting the MIC values and therapeutic response.[61] Colistin is recommended in combination therapy in patients with KPC-Kp infection; however, this still represents a risk for emerging KPC-Kp colistin resistance, as there is currently no molecular method available to detect it.

## Treatment

At the moment, there is no antibiotic scheme regarded as the "gold standard" for KPC-Kp infections. The choice of treatment depends upon the site of serious infection, type of carbapenemase, and the susceptibility profile of the isolate. In critically-ill patients, there is evidence to suggest that combined therapy is preferable to monotherapy. Many reports, including large retrospective cohort studies, have demonstrated that more treatment failures and higher mortality rates are associated with monotherapy antibiotic schemes consisting of polymyxin (colistin), carbapenems, tigecycline and gentamicin. Receiving combinatory therapies with at least two drugs with tested CML activity has shown greater effectiveness in critically-ill patients. The association of meropenem with other antibiotics is important and beneficial when the KPC-Kp isolate has a MIC of meropenem $\leq$ 8mg/L;[62] however, in β-lactam antibiotics, is important to maintain antibiotic exposure. Enhancement of fT>MIC could be achieved using either continuous, total daily dose infused over a 24 hr period or prolonged infusions.[20]

Ceftazidime is a third generation cephalosporin that can be used in combination with avibactam (β-lactamase inhibitor) if the organism is a KPC or OXA-48 producer. A second antibiotic, such as carbapenem, can be added if both isolates have MICs near the susceptibility breakpoint. Using this antibiotic combination could yield positive results and should be considered when treating serious infections due to these pathogens;[63–65] however, resistance has emerged in KPC-3-producing *K. pneumoniae*, pointing to a failure in combinatory treatment. In this case, a more exhaustive analysis should have been performed during the course of treatment in order to rapidly respond and change the antibiotic combination.[66,67] Recently, the combination of meropenem with vaborbactam (formerly RPX7009), a novel cyclic boronic acid-based beta-lactamase inhibitor, was found to potentiat the activity of meropenem. This combination may be more suitable for treating severe drug resistant gram-negative infections as it shows higher rates of clinical effectiveness. The body of evidence surrounding the combination of meropenem and vaborbactam is still limited compared to ceftazidime-avibactam. Recently, other agents (imipenem-relebactam, plazomicin, and cefiderocol) have begun to be evaluated in clinical trials, and the results from these studies are expected to improve clinical response and its application in ASP.[68] Other potential active drugs for treating KPC-Kp include classic and new combinations of aminoglycosides, tigecycline, fosfomycin, and the Eravacycline, a fully-synthetic fluorocycline antibiotic, which is used in complicated intra-abdominal infections.[69,70] Uncomplicated and complicated urinary tract infections caused by KPC-Kp are frequently reported in hospital settings; however, there is no evidence about the best antibiotic regimen for its treatment. It may be possible to include aminoglycoside alone or to use on combination with fosfomycin or doxycycline, as it has shown promising results for treating this type of infection.[70]

## Conclusion

This review provides relevant information for clinical practitioners about the state of the literature on KPC-Kp and current diagnostic tests for its detection. We suggest that healthcare professionals use the key points presented in this review in order to precisely identify and treat KPC-Kp infections. Understanding the genetic underpinnings of antibiotic resistance, its clinical manifestations, and standard diagnostic procedures in CMLs will prevent outbreaks and provide healthcare practitioners and scientists with evidence for understanding KPC-Kp dynamics and epidemiology.

## Abbreviations

Cp-Kpn, carbapenemase–producing *K. pneumoniae* strains; ASP, antimicrobial stewardship program; Cr-KPN, carbapanem- resistant *K. pneumoniae*; KPC-Kp, KPC–producer *K. pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemase; CML, Clinical microbiology laboratories; ID, infectious disease; MDR, multidrug resistant bacteria; AST, antibiotic susceptibility testing; DD, disk diffusion; BD, broth dilution; AG, antimicrobial gradient; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; VME, very major errors; MA, molecular antibiogram; LOS, length of stay.

## Data Sharing Statement

All data generated in this article and derived data supporting the findings of this study are available from the corresponding author on request.

## Acknowledgements

The authors would like to thank the School of Medicine of the Universidad San Francisco de Quito (USFQ) for its academic and financial support and for encouraging interdisciplinary collaboration. Thanks is also given to Sistemas Médicos (SIME-USFQ) for their interest in providing funds for developing research on clinical practice. We would like to thank Clara Cullen and Heather Vellers for their proof reading, help and availability in editing the article. We especially thank to Ana María Gómez for her scientific and medical support. Authors would like to express their gratitude to: Johanna Vicuña, Paola Yépez, Alfredo Terán, Pablo Morejón, Gabriela Aldas, Carolina Escudero, Jonathan Villacís, Manuel Burbano and Mishell Barreno students of the school of Medicine for their initial support and for pointing out the need of microbiology key points for clinical practice regarding Carbapenem-resistant *Klebsiella pneumoniae*.

## Author Contributions

All authors made substantial contributions to conception, design and interpretation of data; they took part in drafting the article and revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. AC put together the team to address the focus of our article.

## Disclosure

The authors report no conflicts of interest in this work.

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