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Prevalence and Distribution of Multidrug Resistance *Klebsiella Pneumoniae*

Khaled Khuzim[1], Atif Bamagoos[1], Mohamed Morsi M. Ahmed [1,2]

[1]Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, 21589, Saudi Arabia
[2]Nucleic Acids Research Dept., Genetic Engineering, and Biotechnology Research Institute (GEBRI), City for Scientific Research and Technological Applications, Alexandria, Egypt

Correspondence Authors: Khiald Khuzim, Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, 21589, Saudi Arabia.
Email: k.b-2011@hotmail.com

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Abstract

***Klebsiella pneumoniae* is an important opportunistic pathogen that commonly causes nosocomial infections and contributes to substantial morbidity and mortality. The bacteria are not airborne, so you can't contract a *K. pneumoniae* infection by breathing the same air as an infected person. Instead, *K. pneumoniae* is spread through direct person-to-person contact, such as when someone with contaminated hands touches a wound. Infections can also occur through the use of contaminated medical equipment. For example, people on ventilators can contract Klebsiella pneumonia if their breathing tubes are contaminated with the bacteria. Similarly, the use of contaminated intravenous catheters can lead to bloodstream infections. The symptoms of a *K. pneumoniae* infection differ depending on where the infection is located and are similar to symptoms of the same diseases caused by other microbes. For instance, meningitis from *K. pneumoniae* produces the hallmark symptoms of bacterial meningitis, including fever, confusion, neck stiffness, and sensitivity to bright lights. Bloodstream infections (bacteremia and sepsis) from Klebsiella can cause fever, chills, fatigue, light-headedness, and altered mental states. This study aims to investigate the prevalence of multidrug resistance in Klebsiella pneumonia (MDR-KP).**

Keywords: Klebsiella pneumonia, Hospitals, Carbapenem-Resistant, β-lactamase

INTRODUCTION

Klebsiella pneumoniae belongs to the Enterobacteriaceae family and is described as a gram-negative, encapsulated, and non-motile bacterium [1] found in humans and other mammals, colonizing the intestine, skin, nasopharynx, and several environmental niches. Once thought to be harmless, this bacterium has become well-known since it was found to be an opportunistic pathogen. This is responsible for a variety of diseases in humans and animals, such as urinary tract infection, pneumonia, intra-abdominal infection, bloodstream infection, meningitis, and pyogenic liver abscess, and is a prominent nosocomial pathogen. Friedlander found it in the lung of a person with pneumonia and wrote about it in 1882 [2,3].

It is one of a handful of bacteria that are now experiencing a high rate of antibiotic resistance secondary to alterations in the core genome of the organism. Alexander Fleming first discovered resistance to beta-lactam antibiotics in 1929 [4]. A gram-negative bacterium's resistance mechanisms include efflux pumps, membrane permeability, the production of lactamases, the modification of antibiotic targets, and the acquisition of alternative metabolic pathways to those inhibited by the antibiotic. Extended-Spectrum-lactamase (ESBL) production is one of bacteria's most important resistance mechanisms [4].

ESBLs can hydrolyze oxyimino cephalosporins, rendering third-generation cephalosporins ineffective against treatment. Due to this resistance, carbapenems became a treatment option for ESBL. However, in 2013, the CDC reported 9000 infections due to carbapenem-resistant Enterobacteriaceae. *K. pneumoniae* was responsible for almost 80% of those infections. The mechanism of carbapenem resistance has been linked to an up-regulation in efflux pumps, alteration of the outer membrane, and increased production of ESBL enzymes in the organism [5,6]

Antimicrobials have been crucial in decreasing morbidity and mortality from infectious diseases. However, the healthcare system is under threat due to the emergence and spread of multidrug-resistant organisms. In recent decades, antimicrobials have become widespread in all countries, irrespective of income level. [6]. MDROs are resistant to antimicrobial agents, such as lactams (penicillins, cephalosporins, and monobactams), carbapenems, fluoroquinolones, and aminoglycosides. The severity and scope of disease caused by these pathogens vary depending on the population affected and the institution reporting it, but MDRO prevention and control should be a national priority [7]. The increased risk of infection is associated with the severity of the patient's illness and underlying conditions, length of exposure to invasive devices and procedures, increased patient contact with healthcare personnel, and period of stay in the ICU [8]. This study aimed to investigate the prevalence of multidrug resistance in Klebsiella pneumonia (MDR-KP).

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Several mechanisms have been characterized through which bacteria become resistant to antibiotics : (i) the production of enzymes that digest/metabolize the antibiotic; (ii) efflux pumps that eliminate the drug from the cell; (iii) modifications to the cellular target of the antibiotic that prevents binding; (iv) activation of an alternate pathway that bypasses drug action; and (v) particularly for gram-negative bacteria, down-regulation or elimination of transmembrane porins through which drugs enter the cell [10-11].

TREATMENT FOR (MDR-KP)

Multi-drug-resistant *Klebsiella pneumoniae* (MDR-KP) is a significant challenge for physicians. The best treatment option for MDR-KP infections is still not well-founded. Combination therapies, including high-dose tigecycline, fosfomycin, colistin, meropenem, and aminoglycosides, are widely used, with suboptimal results. New antimicrobials targeting MDR-KP have been developed during the last few years and are now at various stages of clinical research [9].

RISK FACTORS OF CARBAPENEM RESISTANT *KLEBSIELLA PNEUMONIAE*

The rise of CR-KP infections in Malaysia has been related to several risk factors, including antibiotic indiscriminate usage and comorbidities. The extensive use of carbapenems as first-line therapy for invasive infections caused by carbapenemase-producing *Klebsiella pneumoniae* is also a risk factor for its development. Antibiotic overuse and abuse, a lack of efficient antibiotic resistance surveillance systems, and a significant influx of people, particularly from neighboring Asian nations such as India, Pakistan, and Bangladesh, are all considered significant risk factors. Tourism and international travel by persons harboring resistant *Klebsiella pneumoniae* strains are well-known risk factors that contribute to the widespread multidrug-resistant *Klebsiella pneumoniae*. Comorbidities, prior carbapenem usage, and other risk factors. With the increasing use of carbapenems in hospitals worldwide,

carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has become an essential threat to public health, and its management and treatment pose a challenge for physicians. Antibiotics, especially carbapenems, and invasive procedures were the major risk factors for carbapenem resistance among patients with *K. pneumoniae* BSIs. Strict control measures should be implemented to prevent the emergence and spread of CRKP [9].

TYPES OF CARBAPENEMASE DETECTION METHODS

Identification of carbapenemases is first based on conventional phenotypic tests, including antimicrobial susceptibility testing, modified-Hodge test, and carbapenemase-inhibitor culture tests. Second, PCR sequencing's molecular characterization of carbapenemase genes is essential [8].

MOLECULAR CHARACTERIZATION OF *KLEBSIELLA PNEUMONIAE*

Only a few research have looked at the possible carbapenem resistance mechanisms in Malaysian *Klebsiella pneumoniae* isolates. At the time of writing, the primary carbapenemases producing resistance in CR-KP in Malaysia were blaNDM and blaOXA-48 enzymes. This is not unexpected considering that these enzymes are the most prevalent causes of CR-KP infections and carbapenemases worldwide. In Malaysia, other carbapenemases and isolates containing *Klebsiella pneumoniae* carbapenemase (IMP and KPC) were uncommon. Research at a university hospital molecularly characterized 13 CR KP isolates, seven of which were blaNDM-1 and six of which were blaIMP-4 even though other resistance genes (blaKPC, blaOXA, blaVIM) were not identified. Another research found, however, that scientists discovered that of the 17 CR-KP isolates examined, 12 (70.6 percent) had the blaOXA-48 gene and the prevalent sequence type was ST101. Interestingly, additional carbapenemases are not frequently seen in Malaysia (blaKPC-2 and blaIMP-8) were also identified [16,22]. Research from Universiti Kebangsaan Malaysia Medical Centre found that the blaNDM-1 gene was present in 89.0 percent of 16 CR-KP isolates. However, NDM variations and other carbapenemase genes were not included in this investigation. Similarly, a 2015 and 2016 study from Universiti Sains Islam Malaysia found that Klebsiella pneumoniae that co-produced NDM-1 and OXA-48 genes were the most common (41%), followed by OXA-48 (35%), NDM-1 (12%), and KPC (6%). A comparable investigation at Hospital Tengku Ampuan Afzan revealed that three out of four CR-KP isolates tested positive for blaNDM. All NDM-positive isolates, however, were also positive for at least one additional -lactamase (CTX, SHM, and TEM). It has been reported that nine (10.3 percent) of the 87 non-repetitive isolates of CR-KP investigated in a Malaysian healthcare facility were positive for OXA-48, seven of which were *Klebsiella pneumoniae*. This is the first research to look at the prevalence of Enterobacteriaceae that produce OXA-48 and OXA-181. Between 2016 and 2017, carbapenemase genes were discovered in 55 of 63 CR-KP isolated strains from a tertiary teaching hospital, with blaOXA-48 (63.5 percent) being the most frequent carbapenemase gene [11].

THE PREVALENCE OF (MDR-KP)

The first identification of the ST11 clone in *K. pneumoniae* occurred in 1997 in France. This clone has been associated with the acquisition of resistance genes to a broad spectrum of antimicrobial agents, as well as to the dissemination of OXA-48, in addition to VIM (Verona Imipenemase), NDM (New Delhi Metallo-β-lactamase), and KPC. The origin of the blaCTX-M-15 gene identified in *K. pneumoniae* in Portugal was clone ST336, and the most recent occurrence in France reported a clonal outbreak involving *K. pneumoniae* isolates recovered from a single hospital in the Picardie region of northern France[12,14]. A resistance caused this outbreak to colistin with OXA-48 and CTXM-15, producing K. pneumoniae type ST11 susceptible only to cefoxitin [15,14].

In Spain, blaOXA-48 and blaCTX-M-15 were responsible for a major outbreak involving 44 patients at a hospital in Madrid from 2009 to 2014[15]. Although in the United Kingdom and Sweden, the only resistance genes identified were NDM-type, with blaNDM-1 being isolated in both countries. Among the NDM isolates identified in the United Kingdom, ST231 was the most common type, along with ST147 and ST273. Strains of *K. pneumoniae* NDM-1 positive can exhibit relatively high clonal diversity. In Sweden and the United Kingdom, clone ST14 was the most frequently observed type. Clone *K. pneumoniae* ST14 has been described as a host for the NDM-1 enzyme and is also a frequent host of CTX-M enzymes. In addition, ST14 is a single locus variant (SLV) of ST15, which often encodes the CTX-M type ESBLs [17,18]. In the European countries, Spain stands out as the site where the largest number of different genes (15 in total) *K. pneumoniae* with resistance to the antibiotic β-lactams. The country where the lowest gene diversity occurred was Greece, where the only isolated gene was blaKPC-2 [19,20].

In Asia and Oceania, 41 different resistance gene types have been identified, and the greatest diversity occurred in China, where 14 of the 41 genes were described. The second country with the greatest diversity of genes was Israel (12 different genes), followed by Turkey (11 genes) and Iran (10 genes). The lowest variety of β-lactam resistance genes occurred in Pakistan (2 genes). Despite the lower diversity, the genes identified in Pakistan, blaKPC, and blaNDM-1, are of great importance for tracking the control of microbial resistance. The first gene is characterized by its wide plasmodial spread, and the second has broad relationships with globalization and population mobility. The blaNDM-1 gene was first identified in 2009 in a Swedish patient of Indian origin, who acquired a urinary tract infection in New Delhi, caused by a strain of *K. pneumoniae* that showed resistance to β-lactam antibiotics [21,22]. Ferreira *et al.* [22] performed a study to investigate the antibiotic resistance profile, pathogenic potential, and the clonal relationships between *K. pneumoniae* isolated from patients and sources at a tertiary care hospital's intensive care units in Brazil. Most of *K. pneumoniae* isolates, 84% were classified as multidrug-resistant with high-level resistance to β-lactams, aminoglycosides, quinolones, tigecycline, and colistin. All the 25 isolates presented extended-spectrum beta-lactamase-producing, including carbapenemase producers, and carried the bla_{KPC} (100%), bla_{TEM} (100%), bla_{SHV} variants 96%, bla_{OXA-1} group (84%) and $bla_{CTX-M-1}$ group (72%) genes. The K2 serotype was found in 4% of the isolates, and the K1 was not reported. The virulence-associated genes reported in the 25 isolates were *mrk*D (96%), *fim*H-1 (88%), *ent*B (100%), *iut*A (40%), *ybt*S (60%). The genes associated with efflux pumps and outer membrane porins found were *AcrAB* (100%), *tol*C (96%), *mdt*K (88%), *Omp*K35 (60%),

and *Omp*K36 (28%). The results reported the presence of high-risk international clones between the isolates[22]. Boszczowski *et al.* (2019) performed a study that included 28 patients infected by ColRKP in a tertiary hospital. The microdilution broth test confirmed isolates with MIC >2 by Vitek 2. The polymerase chain reaction was performed for *bla*KPC, *bla*NDM, *bla*OXA-48 , and *bla*mcr-1 genes in the isolates, and Whole Genome Sequencing was performed in six isolates. 61% of participants were female and the median age was 50. In-hospital and 30-day mortality were 64% and 53%, respectively. Central line-associated bloodstream infections, in addition, bacteremia episodes were 61%. The mean APACHE and Charlson comorbidity index were 16 and 5, respectively. Twenty participants (71%) received at least one active drug, and ten (35%) received two drugs: tigecycline 46%, amikacin 21%, and fosfomycin 3%. Also, 26 were positive for *bla*KPC. Eight different clusters were identified. Four STs were detected (ST11, ST23, ST340, and ST437). Mutations on *pmrA*, *arnB*, *udg*, and *yciM* genes were present in all six isolates submitted to WGS; *lpxM*and *mgrB* mutations were also detected in all but one isolate [23]. Al Johani *et al.* (2010) found that the most frequently isolated organism was *Acinetobacter baumannii*, followed by *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pnemoniae, Stenotrophomonas maltophilia,* and *Enterobacter*. Antibiotic susceptibility patterns significantly declined in many organisms, especially *A baumannii, E coli, S marcescens*, and *Enterobacter*. *A baumannii* susceptibility was significantly decreased to imipenem (55% to 10%), meropenem (33% to 10%), ciprofloxacin (22% to 10%), and amikacin (12% to 6%). *E coli* susceptibility was markedly decreased (from 75% to 50% or less) to cefuroxime, ceftazidime, cefotaxime, and cefepime. *S marcescens* susceptibility was markedly reduced to cefotaxime (100% to 32%), ceftazidime (100% to 35%), and cefepime (100% to 66%). *Enterobacter* susceptibility was markedly decreased to ceftazidime (34% to 5%), cefotaxime (34% to 6%), and piperacillin-tazobactam (51% to 35%). Respiratory samples were the most frequently indicative of multidrug-resistant pathogens (63%), followed by urinary samples (57%) [24]. Al-Tawfiq *et al.* (2007) performed a study and concluded that 3070 distinct isolates of *K. pneumoniae* were tested. Hospital-acquired isolates were more resistant to antibiotics than outpatient isolates. The resistance rates to cefazolin, trimethoprim-sulfamethoxazole, and ciprofloxacin were 10.8%, 5%, and 15.8% for hospital-acquired isolates; and 11%, 9.6%, and 4.4% for outpatient isolates. Resistance to ceftriaxone and ceftazidime was detected in 5.6% and 13.8% of hospital-acquired isolates and 1% and 2.7% of outpatient isolates, respectively. All tested isolates were susceptible to imipenem. Resistance to 3 or more groups of antibiotics was present in 1.7% of the hospital-acquired isolates and 0.6% of the outpatient isolates [25].

CONCLUSION

This research looked at the trends in carbapenem resistance in *Klebsiella pneumoniae* isolates from Malaysian hospitals. According to the data from the numerous hospitals in different locations, the most often observed carbapenemase genes were blaNDM and blaOXA. According to the 2019 national antimicrobial monitoring report, the carbapenem resistance rate for *Klebsiella pneumoniae* was less than 5%. Antimicrobial resistance in *Klebsiella pneumoniae* is a critical issue that must be addressed constantly. Therefore, developing a preventative and control approach is crucial to address this public health danger. This may be achieved by building a signaling system at the hospital through active surveillance to collect epidemiological data, establishing an award for CR-KP-positive patients, and developing restrictions for new patients.

Conflict Of Interest

The authors declared that there is no conflict of interest.

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