# The Situation of Antibiotic Resistance in *Klebsiella Pneumoniae* and Carbapenemase–Producing *Klebsiella Pneumoniae* in Vietnam: A Cross–Sectional Study

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# Abstract

**Objective:** *Klebsiella pneumoniae* (*K. pneumoniae*) is one of the most prevalent human pathogens. Carbapenemaseproducing *klebsiella pneumoniae* (CPKP) has recently developed significant antibiotic resistance, not just to carbapenem antibiotics but also to the majority of other currently available antibiotics. Prior to this point, there have been few international studies or publications on the situation of CPKP in Vietnam. Hence, this study was conducted to determine the antibiotic resistance of *K. pneumoniae* and CPKP strains in Can Tho, Vietnam.

**Material and Methods:** In total, 345 *K. pneumoniae* strains were isolated. Antibiotic susceptibility was assessed via an automated microbiological system. A modified carbapenem inactivation assay was applied to identify CPKP strains, followed by the use of the MASTDISCS combi Carba plus disc system to classify certain carbapenemases.

**Results:** Of the 345 *K. pneumoniae* strains, 110 represented an isolation rate of 31.9%. There was a significant correlation (p-value<0.05) between the specimen type, hospital unit and CPKP ratio. All the examined CPKP strains exhibited

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complete resistance to penicillin and cefazolin. The CPKP strains were also significantly more resistant to PTZ, cefepime, ciprofloxacin and imipenem than the non-CPKP strains (p-value<0.05). Amikacin, gentamicin and TMP/SMX have been shown to be effective in treating patients infected with CPKP strains.

**Conclusion:** CPKP accounts for 31.9% of all *K. pneumoniae* infections. *K. pneumoniae* and CPKP exhibited the highest levels of resistance to ampicillin, cefazoline, ciprofloxacin, ceftriaxone and ceftazidime. Amikacin, gentamicin and TMP/SMX were the least resistant antibiotics tested.

Keywords: antibiotic resistance, carbapenem resistance, carbapenemase-producing klebsiella pneumoniae, klebsiella pneumoniae, Vietnam

## Introduction

Klebsiella pneumoniae (K. pneumoniae) is a type of gram-negative bacteria, and is the most significant member of the genus klebsiella (enterobacteriaceae). Humans are the primary hosts for K. pneumoniae. In general, the main sources of enterobacteriaceae infection are the gastrointestinal tract of patients and the hands of hospital personnel<sup>1</sup>. K. pneumoniae is also a common cause of several other infections; including: pneumonia, urinary tract infections, cutaneous infections, and septicemia<sup>2,3</sup>. A systematic review and meta-analysis of the global burden of bacterial antimicrobial resistance in 2019, revealed that K. pneumoniae ranked third among all pathogens in terms of deaths associated with resistance; just behind escherichia coli and staphylococcus aureus. In addition, carbapenem and cephalosporin-resistant K. pneumoniae play significant roles<sup>4</sup>.

The resistance mechanisms of *K. pneumoniae* include the production of  $\beta$ -lactamases, lack of membrane porin proteins, and active efflux of antibacterial drugs<sup>5</sup>. The majority of *K. pneumoniae* bacteria can produce the extended spectrum  $\beta$ -lactamase (ESBL), which inactivates broad-spectrum cephalosporins and most b-lactams. Additionally, they are cross-resistant to numerous other antibiotic classes; including aminoglycosides and

fluoroquinolon<sup>6,7</sup>. Therefore, carbapenem antibiotics are considered the last choice of treatment. However, this group of antibiotics has been subjected to the selection pressure of *K. pneumoniae* in Vietnam owing to the lack of control over their use. The production of the carbapenemase enzyme is the primary cause of widespread antibiotic resistance, not only to carbapenem antibiotics but also to most other currently available antibiotics<sup>8</sup>.

The status of carbapenemase-producing *K*. *pneumoniae* (CPKP) has been constantly studied, and updated to provide physicians with effective treatment options. In 2014, Ghotaslou et al. conducted a study in five hospitals in Iran, which revealed that the prevalence of CPKP was 26.3% of all *K. pneumoniae* infections<sup>9</sup>. Moreover, this proportion has been reported to be nearly twice as high in France and the United States (57.1% and 45.4%, respectively)<sup>10,11</sup>. In China, Wang et al. (2018) described the characteristics of carbapenem-resistant Enterobacteriaceae, and showed that 91% of cases were caused by CPKP<sup>12</sup>.

In Vietnam, as of 2015, *K. pneumoniae* has attracted attention in clinical practice, with the data revealing that the prevalence of antibiotic-resistant *K. pneumoniae* has increased over the years. In 2017, a study on the antibiotic resistance rate of *K. pneumoniae* revealed

that cephalosporin resistance ranged from 22.9% to 54.7%; whereas, carbapenem resistance accounted for  $3.5\%^{13}$ . In 2019, these rates increased to 78.1%-83.8% for cephalosporin resistance and 38.4% for imipenem resistance; a common antibiotic from the carbapenem class<sup>14</sup>. To date, there have been few studies or international publications on the situation of CPKP in Vietnam. Due to this knowledge gap, this study was conducted to determine the antibiotic resistance rates of *K. pneumoniae* and CPKP in Can Tho, Vietnam.

### **Material and Methods**

### Study setting

From June 2021 to May 2022, a cross-sectional study, involving 345 *K. pneumoniae*-infected patients, at the Can Tho General Hospital and Can Tho Central General Hospital was conducted. Can Tho is the central city that represents the Mekong Delta region of Vietnam, and these two hospitals are classified as first-class hospitals, with contemporary facilities in order to provide inhabitants with comprehensive healthcare services. Can Tho General Hospital is an 800-bed hospital belonging directly to the Can Tho Department of Health. Can Tho Central General Hospital has a capacity of 1200 beds, and is directly affiliated with the Ministry of Health of Vietnam. The teams from both hospitals collaborated to collect and analyze all samples in accordance with an established process.

### Patients and data collection

*K. pneumoniae* was isolated from patients with infectious diseases, who were older than 16 years: all patients provided consent to participate in the study. If more than one *K. pneumoniae* specimen was isolated from a patient, only one specimen was selected for analysis in this study. Exclusion criteria were: *K. pneumoniae* strains that were isolated from the same patient later in the treatment

course, *K. pneumoniae* strains that were contaminated in patient samples, or were isolated to monitor nosocomial infections and periodic cultures, and patients who did not complete an antibiogram; or whose antibiogram did not contain sufficient antibiotics for the study. According to a previous study conducted in Vietnam, the rate of CPKP isolated from all *K. pneumoniae* samples was 26.4%<sup>15</sup>. The calculated sample sizes for this study was in accordance with the World Health Organization sample size calculation program (version 2.00), with  $\alpha$ =0.05 and  $\varepsilon$ =relative accuracy (0.25)=1.96. The calculation yielded a sample size of 299 samples; in total, 345 samples were collected.

Infectious disease physicians collected sociodemographic and clinical data (age, gender, admission date, and specimen collection date) as well as the samples. Urine, blood, sputum, pus and other biological fluids were collected to identify pathogen characteristics and antibiotic resistance rates. Bacteria were initially cultured from sputum, urine, blood, pus and other biological fluids. The isolation was performed according to the following procedure.

**Blood specimens:** Blood culture bottles were incubated at 37 °C in an incubator for 7 days to determine whether there was bacterial development in the solid phase. The liquid phase was coated with the solid phase when no bacteria developed. Because of some bacteria blind cultures were performed over two days (the second and sixth days) on blood agar (BA) incubated in a CO<sub>2</sub> incubator or a candle jar for 24 hr. A Gram-stained smear identification of the bacteria and an antibiogram were performed whenever there was evidence of bacteria growing on the solid phase or the blind cultures on BA<sup>16</sup>.

**Urine specimens:** Culture rings were filled using a 1  $\mu$ I quantitative inoculation tip and the sample was spread evenly across the surface of a culture agar dish (BA and MacConkey (MC)). Then, the BA was incubated in a candle jar for 24 hr and the MC was incubated in an incubator at 37 °C for 24 hr. The number of colonies (n) per agar dish were counted to obtain the total number of live bacteria (colony-forming units, CFU) in 1 ml of urine: X (CFU/ml)=n×1,000<sup>17</sup>. The results were as follows: (1) X<10,000 CFU/ml, no urinary tract infection (UTI); (2) 10,000  $\leq$ X $\leq$ 100,000 CFU/ml, suspected UTI; and (3) X>100,000 CFU/ml, UTI. Suspected UTI specimens were reported to the physician for resampling, or to continue the investigation if the patient had a medical history of repeated UTIs.

Sputum specimens: Before bacterial culture, isolation, and identification, it was crucial to evaluate whether the sputum samples were reliable based on the Bartlett scale<sup>18</sup>. First, 1 ml of sputum was added to 1 ml of normal saline and vortexed thoroughly to dissolve it. Next, 1 ml of the dissolved sputum solution was diluted in 9 ml of 0.9% NaCl solution and mixed thoroughly. Finally, quantitative cultures were performed on an MC medium, with 1µl solution above and incubated at 35 °C for 24 hr or on a BA medium incubated at 35  $^{\circ}\text{C}$  for 24 hrs, with 5-7% CO  $_{\rm o}$ . After 24 hr, colony morphology was observed and the suspected pathogenic bacteria were selected and counted using the following formula: X (CFU/ml)=n×2×10×1,000; where: "n" is the number of suspected colonies, "2" is the first-step dilution factor, "10" is the second-step dilution factor and "1,000" is the final dilution factor<sup>19</sup>.

**Pus and other biological fluid specimens:** Specimens were collected using sterile cotton swabs, and were immediately transported to the laboratory. They were then inoculated into liquid BHI medium for 1 hr at 37 °C. This was then continued with 3D inoculation on BA medium incubated in a candle jar at 37 °C for 24 hr or on MC medium incubated at 37 °C for 24 hr<sup>20</sup>.

Staining and observation was then performed to identify the results of bacteria. Using an automated microbiology system (BD Phoenix, Becton Dickinson) and a VITEK<sup>®</sup> 2 system, at Can Tho Central General Hospital and Can Tho General Hospital, respectively, the bacteria were identified, and their antibiotic susceptibility was determined. A modified carbapenem inactivation method (mCIM) assay was used to screen CPKP strains. To determine CPKP by mCIM with CLSI 2020, the bacterial control strains were used; including Escherichia coli ATCC 25922 as the standard sensitive carbapenem strain, *K. pneumoniae* ATCC BAA 1705 as the positive control and *K. pneumoniae* ATCC BAA 1706 as the negative control. Following this, MASTDISCS combi<sup>TM</sup> Carba Plus (D73C) (Mast Group, US) method was used to classify carbapenemases<sup>21,22</sup> (Figure 1).

### Statistical analysis

The data were analyzed using SPSS 18.0. A chisquared test was used to compare the differences in the two ratios between groups of patients with similar study characteristics; including: gender, age group, department and specimen. A p-value≤0.05 was considered as statistically significant.

### **Results**

A total of 345 patients participated in this study. Males made up 57.4% (198/345) of the total population and females accounted for 42.6% (147/345). In this study, the average age was 65.4 years of age, with 67.2% (232/345) of the participants being over 60 years of age. We collected samples from the majority of hospital departments and classified them into four categories: surgery, internal medicine, anesthesiology and the intensive care unit (ICU). The prevalence of *K. pneumoniae* infections was the highest in the internal medicine group (46.4%), followed by the ICU group (36.0%). The surgery group had the lowest prevalence rate of 7.2%. Overall, 55.4% of the isolated *K. pneumoniae* specimens in this study were from sputum, while 21.4% were from pus: blood samples represented the lowest percentage (4.1%) (Table 1).



Figure 1 A schematic diagram of our data collection procedure

CPKP was isolated from 110 samples, representing 31.9% of the total number of samples. Female patients had a higher prevalence of CPKP (33%) compared to male patients, who had a prevalence rate of 30.8%. However, the difference between the male and female rates was not significant. The 16–45 years age group had the highest CPKP percentage at 34.3%, while the 46–60 years age group had the lowest percentage (29.0%). The differences in the distributions of CPKP isolation between gender and age groups were insignificant. The proportion of CPKP-isolated specimens was the highest in the surgery group (44%). The rate of CPKP was highest in blood samples (64.3%) and lowest in pus samples (13.5%). In addition, the distribution of CPKP varied significantly between departments and specimen types (Table 2).

In terms of CPKP distribution among the 110 isolates, the highest percentages were attributable to the following conditions: male gender, 55.4% (61/110); age>60 years, 68.1% (75/110); sputum sample, 57.2% (63/110); and the ICU department group, 48.1% (53/110) (Table 2). Additionally, OXA-48 accounted for 72.7% (80/110) of the 110 CPKP isolates, followed by MBL at 12.7% (14/110), and KPC at 8.2% (9/110) (Figure 2).

	Ν	Percentage		
Gender				
Male	198	57.4		
Female	147	42.6		
Age group (Mean age=65.4±15.9)				
16-45 years old	35	10.1		
46-60 years old	78	22.6		
>60 years old	232	67.3		
Department				
Surgery	25	7.2		
Internal medicine	160	46.4		
Anaesthesiology	33	9.6		
Intensive care unit	127	36.8		
Specimen				
Sputum	191	55.4		
Pus	74	21.4		
Blood	14	4.1		
Urine	38	11.0		
Biological fluid	28	8.1		

#### Table 1 The characteristics of the study participants

K. pneumoniae was resistant to over 50% of the antibiotics in this study (8/12). K. pneumoniae had the highest level of resistance to ampicillin; a member of the penicillin family. The rate of resistance to the cephalosporins was high. For example, cephazolin (1<sup>st</sup> generation), ceftazidime (3<sup>rd</sup> generation), ceftriaxone (3<sup>rd</sup> generation) and cefepime (4<sup>th</sup> generation) had resistance rates of 76.5%, 67.5%, 68.1%, and 61.2%, respectively. There was an average resistance rate of 52.2% to piperacillin-tazobactam (PIP/TAZO); an antibiotic with  $\beta$ -lactamase inhibitors. A high resistance rate of 69.9% (241/345) to ciprofloxacin; a member of the fluoroquinolone class, was observed. The rate of resistance to the carbapenem group of antibiotics; including imipenem and ertapenem, was between 43.2% and 49.0%; whereas, resistance to amikacin was the lowest at 17.4% (60/345) (Figure 3).

# Table 2The distribution of carbapenemase-producing<br/>klebsiella pneumoniae (CPKP) among total<br/>klebsiella pneumoniae infections

	CPKP % (n)	Non-CPKP % (n)	p-value
Gender			
Male	30.8 (61)	69.2 (137)	
Female	33.3 (49)	66.7 (98)	0.619
Age group (Mean age=	65.4±15.9)		
16-45 years old	34.3 (12)	65.7 (23)	
46-60 years old	29.5 (23)	70.5 (55)	0.852
>60 years old	32.3 (75)	67.7 (157)	
Department			
Surgery	44.0 (11)	56.0 (14)	
Internal medicine	26.2 (42)	73.8 (118)	0.001
Anesthesiology	12.1 (4)	87.9 (29)	<0.001
Intensive care unit	41.7 (53)	58.3 (74)	
Specimen			
Sputum	33.0 (63)	67.0 (128)	
Pus	13.5 (10)	86.5 (64)	
Blood	64.3 (9)	35.7 (5)	<0.001
Urine	50.0 (19)	50.0 (19)	
Biological fluid	32.1 (9)	67.9 (19)	
Total	31.9 (110)	68.1 (235)	

CPKP=carbapenemase-producing klebsiella pneumoniae

CPKP strains exhibited the lowest levels of resistance to amikacin (32.7%), gentamicin (47.3%), and TMP/SMX (61.8%). However, 100% of the CPKP strains were resistant to ampicillin and cefazolin. Additionally, the CPKP strains exhibited almost complete resistance to the other antibiotics considered in this experiment. The rates of resistance of CPKP to PIP/TAZO, cefepime, amikacin, ciprofloxacin and imipenem were statistically significant (p-value<0.05) compared to those of the non-CPKP isolates (Table 3).



OXA-48=oxacillinase-48, MBL=mannose-binding lectin, KPC=klebsiella pneumoniae carbapenemase

Figure 2 The distribution of carbapenemase-producing klebsiella pneumoniae (CPKP) by carbapenemase

# Discussion

This study included 345 patients, with a greater proportion of men than women (57.4% vs 42.6%, respectively). This was consistent with previous pilot studies in Vietnam that involved a greater proportion of men than of women. Therefore, it is believed that this represents the gender characteristics of K. pneumoniae infections in Vietnam. Nirwati et al. reported in 2019, that males accounted for 64.07% of their study population at the Klaten Hospital in Indonesia; while females accounted for 35.59%<sup>23</sup>. In a 2020, study at the Côte d'Ivoire Hospital, Schultea et al. also reported a higher proportion of males than females  $(59.8\% \text{ vs. } 40.2\%)^{24}$ . The average age in this study was 65.4 years, with a minimum of 18 years and a maximum of 99. The older than 60 years group had the highest prevalence rate at 67.2% (232/345), and this rate gradually decreased with age. This result is comparable to

those of other Asian nations<sup>23,25</sup>. Advanced age is most likely a risk factor for patients with *K. pneumoniae* vulnerability. Therefore, in cases of infections that require hospitalization, special care must be given to elderly patients.

Similar to the aforementioned studies, the samples with the highest frequency of *K. pneumoniae* were sputum samples (55.4%; 191/345), followed by pus samples  $(21.4\%)^{23.25}$ . Each type of specimen had a distinct group of infectious diseases. From this, it was evident that respiratory infections were frequently caused by *K. pneumoniae*; therefore, it is necessary to focus on infection control; particularly the control of airborne infections, to avoid the spread of *K. pneumoniae* in hospital environments. Additionally, the ICU and internal medicine groups had high prevalence rates of *K. pneumoniae* (36.8% and 46.4%, respectively), particularly in the respiratory division. Because *K. pneumoniae* is a common cause of nosocomial infections,



PIP/TAZO=piperacillin/tazobactam, TMP/SMX=trimethoprim/sulfamethoxazole



the highest prevalence rates were observed in departments with large numbers of critically ill patients requiring long hospitalization periods and invasive procedures, which could easily increase the risk of infection with *K. pneumoniae*. This result is comparable to those of other prior studies<sup>25-27</sup>.

In terms of carbapenemase production, 33.3% (49/147) of *K. pneumoniae* samples from female patients produced carbapenemase, compared to 30.8% (61/198) of samples from male patients. CPKP prevalence was highest among individuals aged 16–45 years (34.3%; 12/35) and

lowest among patients aged 46–60 years (29.5%; 23/78). Thus, this study differs from previous international research. According to findings from a study conducted by Jeong at five hospitals in Korea in 2016, the prevalence of CPKP infection was predominantly among male patients (76.8%), with an average age of 64.6 years<sup>28</sup>. In the same year, Shimasaki conducted research at a long-term acute care hospital in Chicago and found that 41.6% of patients infected with CPKP strains were female, while 58.2% were male. The median patient age in that study was 63.2 years<sup>29</sup>.

**Table 3** The antibiotic-resistance rates of carbapenemase-producing klebsiella pneumoniae (CPKP) andnon-CPKP isolations

Antibiotic	CPKP % (n=110)	non-CPKP % (n=235)	p-value
Piperacilin/tazobactam	97.3	31.1	0.00
Ampicillin	100	99.1	>0.05
Cefazolin	100	65.5	
Ceftazidime	99.1	52.8	
Ceftriaxone	98.2	54.0	
Cefepime	97.3	44.3	0.00
Amikacin	32.7	10.2	0.00
Gentamicin	47.3	37.4	
Ciprofloxacin	99.1	56.2	0.00
TMP/SMX	61.8	52.3	>0.05
Imipenem	94.5	19.1	0.00
Ertapenem	99.1	25.5	

CPKP=Carbapenemase-producing *klebsiella pneumoniae*, TMP/ SMX=trimethoprim/sulfamethoxazole

Consequently, gender and age characteristics have changed at various points in time, and in various study locations.

Among the 110 strains (57.3%, 63/110), sputum samples showed the highest incidence of CPKP. There was a correlation between the CPKP strains and specimen types (p-value<0.001). According to Jeong, CPKP prevalence was the highest in respiratory specimens (44.9%) in 2016<sup>28</sup>. This result was also in line with the fact that the majority of *K. pneumoniae* bacteria were found in the respiratory samples in this study. Similar to the results for *K. pneumoniae* as a whole, the ICU department had the highest rate of CPKP prevalence (48.1%; 53/110), which correlated with the department (p-value<0.001). According to domestic and international investigations, the majority of CPKP strains were identified in Intensive Care Unit samples<sup>9,28</sup>.

Carbapenems are used as a last resort for the treatment of serious infections. Carbapenemases are

enzymes that hydrolyze carbapenems and are the primary cause of carbapenem resistance. According to the Ambler classification, carbapenemases are classified into three types, based on their chemical structure<sup>30</sup>. In particular, carbapenemases KPC (class A), metal-β-lactamases VIM, NDM (MBL, class B) and OXA-48 (class D) have been focused on carbapenems resistance<sup>31,32</sup>. According to this research, of the 110 strains of CPKP; OXA-48 (group D) had the highest prevalence at 72.7% (80/110), followed by MBL (group B) at 12.7% (14/110), KPC (group A) at 8.2% and other carbapenemases at 6.4% (7/110). These findings were comparable to those of Messaoudi, who conducted research in 2014, at Sahloul-Sousse University Hospital in Tunisia, and found that the prevalence rate of CPKP group D (OXA-48) was 84.0%; while the prevalence rate of group B (MBL) was 7.0%<sup>33</sup>. In contrast, a study by Ghotaslou et al. in Iran found that CPKP strains had the highest proportion of MBL (class B) at 15.8%, followed by KPC (class A) at 7.0% and OXA-48 (class D) at 3.5%9.

In this investigation, K. pneumoniae was resistant to more than 50% of the antibiotics evaluated. K. pneumoniae was the most resistant to ampicillin among the penicillinbased antibiotics (343/345). The overall resistance rate of K. pneumoniae to cephalosporin antibiotics ranged from 61.2% to 76.5%. Haing a resistance rate of 76.5% (264/345), K. pneumoniae exhibited the highest level of resistance to cefazolin: the first generation of cephalosporins. K. pneumoniae resistance to the third and fourth generations of cephalosporins ranged from 61.2% to 68.8%. The average resistance rate of *K. pneumoniae* to the group of antibiotics coupled with  $\beta$ -lactamase inhibitors was 52.2% (180/345 for piperacillin-tazobactam). K. pneumoniae was highly resistant to ciprofloxacin, at a rate of 69.9% (241/345). In the folate pathway inhibitor group, the average rate of resistance to trimethoprim-sulfamethoxazole was 55.4% (191/345). K. pneumoniae resistance to carbapenems

ranged between 43.2% and 49.0% on average. The antibiotic to which K. pneumoniae showed the lowest rate of resistance was amikacin (17.4%; 60/345). K. pneumoniae exhibited a resistance rate of 40.6% (140/345) to gentamicin. Similarly, a study by Al-Zalabani at King Fahad Hospital, Saudi Arabia from 2014 to 2018 found a typical K. pneumoniae antibiotic resistance rate of 58.7% for piperacillin-tazobactam, 99.9% for ampicillin, 77.8% for ceftriaxone, and 38.8% for imipenem<sup>34</sup>. A more recent clinical profile of K. pneumoniae in Portugal demonstrated a higher rate of  $\beta$ -lactam resistance than that in Vietnam. Cefazolin, cefepime, ceftazidime and PIP/TAZO were almost completely resistant. Furthermore, the rates of resistance to imipenem (67.6%) and ertapenem (76.5%), which are both members of the carbapenem family, were much higher in this study<sup>35</sup>. In addition, based on the global meta-analysis by Uzairue et al., the rate of carbapenem resistance in K. pneumoniae is average; including resistance to ertapenem (44.4%), imipenem (35.2%), and meropenem (36%). However, the rate of amikacin resistance in K. pneumoniae in this study's investigation was still lower than the rate of 25.4% identified in the meta-analysis<sup>36</sup>.

In this study, 100% of CPKP strains were resistant to ampicillin and cefazolin. CPKP strains showed the lowest levels of resistance to amikacin (32.7%), gentamicin (47.3%), and TMP/SMX (61.8%). The CPKP strains also exhibited almost complete resistance to the other antibiotics tested. The CPKP strains were much more resistant to the tested antibiotics than non-CPKP strains. These results were similar to those of a 2015, Taiwanese study by Chiu, which demonstrated that CPKP strains had the least resistance to amikacin (21.2%) and gentamicin (46.0%), had relatively high resistance to TMP/SMX (70.9%), and were nearly completely resistant to other antibiotics in the trial<sup>37</sup>. In a 2017 study, conducted in Bangladesh by Okanda et al., the total resistance of CPKP to several antibiotics was comparable to that observed in this study. In contrast, the prevalence of resistance to amikacin (86%), gentamycin (100%), and TMP/SMX (86%) is inversely high<sup>38</sup>. In 2022, a study in Wuhan, China discovered a similarity in CPKP resistance to some commonly used antibiotics; including ampicillin, ciprofloxacin, ceftriaxone, imipenem and PIP/TAZ, with 100% resistance. However, this study found a significantly higher rate of resistance to amikacin and gentamicin, which were still susceptible in this study, with 86.67% for each<sup>39</sup>.

These results could contribute to improvements in the administration of antibiotics during the clinical practice of local physicians, and help fill the knowledge gap regarding the situation of CPKP in Vietnam. These results also show that it is crucial to restrict the widespread use of carbapenems to treat *K. pneumoniae*–infected individuals. In addition, the antibiotics amikacin, gentamicin and TMP/ SMX have been demonstrated to be useful in treating patients infected with CPKP strains; however, MBL–type CPKP strains are not recommended.

### Conclusion

*K. pneumoniae* is one of the most important pathogens associated with multidrug resistance deaths. In this study, CPKP was highly resistant to several antibiotics and accounted for 31.9% of all *K. pneumoniae* infections. *K. pneumoniae* was the least resistant to amikacin, gentamicin and TMP/SMX in general, and CPKP in particular. The most resistant antibiotics were ampicillin, cefazolin, ciprofloxacin, ceftriaxone and ceftazidime. The detection of carbapenemase–encoding genes and other CPKP resistance genes in Vietnam should be investigated further.

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# **Conflict of interest**

The authors declare that they have no competing interests.

### References

- Ashurst JV, Dawson A. *Klebsiella pneumoniae*. Florida: StatPearls; 2022.
- Navon-Venezia S, Kondratyeva K, Carattoli A. *Klebsiella pneumoniae*: a major worldwide source and shuttle for antibiotic resistance. FEMS Microbiol Rev 2017;41:252–75.
- Tran HD, Bach Nguyen YT, Thanh Tran T, Thu Le TT, Thu Nguyen HT, Minh Nguyen C, et al. Community-acquired pneumonia-causing bacteria and antibiotic resistance rate among Vietnamese patients: a cross-sectional study. Medicine (Baltimore) 2022;101:e30458.
- Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399:629– 55.
- Lin Z, Yu J, Liu S, Zhu M. Prevalence and antibiotic resistance of *klebsiella pneumoniae* in a tertiary hospital in Hangzhou, China, 2006–2020. J Int Med Res 2022;50:03000605221079761.
- Padmini N, Ajilda AAK, Sivakumar N, Selvakumar G. Extended spectrum β-lactamase producing escherichia coli and *klebsiella pneumoniae*: critical tools for antibiotic resistance pattern. J Basic Microbiol 2017;57:460–70.
- Do Tran H, Trung Nguyen B, Quang Tran H, Gia Tran H. A cross-sectional study of the antibiotic resistant prevalence of ESBL-producing enterobacteriaceae in Vietnam. J Health Sci 2022;12:184–8.

- Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević AT, et al. Occurrence of carbapenemaseproducing *klebsiella pneumoniae* and escherichia coli in the European survey of carbapenemase-producing enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis 2017;17:153–63.
- Ghotaslou R, Sadeghi MR, Akhi MT, Hasani A, Asgharzadeh M. Prevalence and antimicrobial susceptibility patterns of ESBL, AmpC and carbapenemase-producing enterobactericeae isolated from hospitalized patients in Azerbaijan, Iran. Iran J Pharm Res 2018;17(Suppl):79–88.
- Dortet L, Cuzon G, Ponties V, Nordmann P. Trends in carbapenemase-producing enterobacteriaceae, France, 2012 to 2014. Euro Surveill 2017;22:30461.
- Shimasaki T, Seekatz A, Bassis C, Rhee Y, Yelin RD, Fogg L, et al. Increased relative abundance of carbapenemaseproducing *klebsiella pneumoniae* within the gut microbiota is associated with risk of bloodstream infection in long-term acute care hospital patients. Clin Infect Dis 2019;68:2053–9.
- Wang Q, Wang X, Wang J, Ouyang P, Jin C, Wang R, et al. Phenotypic and genotypic characterization of carbapenemresistant enterobacteriaceae: data from a longitudinal large-scale CRE study in China (2012–2016). Clin Infect Dis 2018;67(Suppl 2):S196–205.
- Quoc Trung N, Thai Binh P, Phuong Linh V, Minh Nga C. Surveying in vitro effectively in combination with some antibiotics against multidrug-resistant of escherichia coli and *klebsiella pneumoniae*. Ho Chi Minh City J Med 2019;23:100–6.
- Truong Phu D, Ngoc Cua L, Vinh Nien L, Van Mai D. Current situation of antibiotic resistance of *klebsiella pneumoniae* at Can Tho Central General Hospital in 2019. Can Tho J Med Pharm 2020;30:115–21.
- Thai Duong V, Hoang Long D, Thi Dieu Hien N. Study on Wide-spectrum β-lactamase-producing escherichia coli Isolated at Can Tho Central General Hospital. Vietnam Med J 2022;518:87-91.
- Ombelet S, Barbé B, Affolabi D, Ronat J-B, Lompo P, Lunguya O, et al. Best practices of blood cultures in low- and middleincome countries. Front Med (Lausanne) 2019;6:131.
- Karah N, Rafei R, Elamin W, Ghazy A, Abbara A, Hamze M, et al. Guideline for urine culture and biochemical identification of bacterial urinary pathogens in low-resource settings. Diagnostics (Basel) 2020;10:832.

- Popova G, Boskovska K, Arnaudova–Danevska I, Smilevska– Spasova O, Jakovska T. Sputum quality assessment regarding sputum culture for diagnosing lower respiratory tract infections in children. Open Access Maced J Med Sci 2019;7:1926–30.
- Schumacher SG, Wells WA, Nicol MP, Steingart KR, Theron G, Dorman SE, et al. Guidance for studies evaluating the accuracy of sputum-based tests to diagnose tuberculosis. J Infect Dis 2019;220(Suppl 3):S99–107.
- Giuliano C, Patel CR, Kale-Pradhan PB. A guide to bacterial culture identification and results interpretation. P T 2019;44:192– 200.
- Clinical and Laboratory Standards Institute. Preformance standards for antimicrobial susceptibility testing; Thirty infomational supplement, M100-S30. 30<sup>th</sup> ed. Pennsylvania: Clinical and Laboratory Standards Institute; 2020.
- European Centre for Disease Prevention and Control (ECDC). Laboratory manual for carbapenem and colistin resistance detection and characterisation for the survey of carbapenemand/or colistin-resistant Enterobacteriaceae, Version 2.0. Stockholm: ECDC; 2019.
- Nirwati H, Sinanjung K, Fahrunissa F, Wijaya F, Napitupulu S, Hati VP, et al. Biofilm formation and antibiotic resistance of *klebsiella pneumoniae* isolated from clinical samples in a tertiary care hospital, Klaten, Indonesia. BMC Proc 2019;13(Suppl 11):20.
- Müller-Schulte E, Tuo MN, Akoua-Koffi C, Schaumburg F, Becker SL. High prevalence of ESBL-producing *klebsiella pneumoniae* in clinical samples from central Côte d'Ivoire. Intl J Infect Dis 2020;91:207–9.
- 25. Wang C, Yuan Z, Huang W, Yan L, Tang J, Liu CW. Epidemiologic analysis and control strategy of *klebsiella pneumoniae* infection in intensive care units in a teaching hospital of People's Republic of China. Infect Drug Resist 2019;12:391–8.
- Cao Z, Yue C, Kong Q, Liu Y, Li J. Risk factors for a hospital-acquired carbapenem-resistant *klebsiella pneumoniae* bloodstream infection: a five-year retrospective study. Infect Drug Resist 2022;15:641–54.
- Zhang J, Li D, Huang X, Long S, Yu H. The distribution of *k. pneumoniae* in different specimen sources and its antibiotic resistance trends in Sichuan, China From 2017 to 2020. Front Med (Lausanne) 2022;9:759214.

- Jeong SH, Kim HS, Kim JS, Shin DH, Kim HS, Park MJ, et al. Prevalence and molecular characteristics of carbapenemaseproducing enterobacteriaceae from five hospitals in Korea. Ann Lab Med 2016;36:529–35.
- Shimasaki T, Seekatz A, Bassis C, Rhee Y, Yelin RD, Fogg L, et al. Increased relative abundance of *klebsiella pneumoniae* carbapenemase-producing *klebsiella pneumoniae* within the gut microbiota is associated with risk of bloodstream infection in long-term acute care hospital patients. Clin Infect Dis 2019;68:2053–9.
- Pfeifer Y, Cullik A, Witte W. Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. Int J Med Microbiol 2010;300:371–9.
- Sarowska J, Choroszy-Krol I, Jama-Kmiecik A, Maczynska B, Cholewa S, Frej-Madrzak M. Occurrence and characteristics of carbapenem-resistant *klebsiella pneumoniae* strains isolated from hospitalized patients in Poland-a single centre study. Pathogens 2022;11:859.
- Logan LK, Weinstein RA. The epidemiology of carbapenemresistant enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis 2017;215(suppl 1):S28–36.
- 33. Messaoudi A, Mansour W, Jaidane N, Chaouch C, Boujaâfar N, Bouallègue O. Epidemiology of resistance and phenotypic characterization of carbapenem resistance mechanisms in *klebsiella pneumoniae* isolates at Sahloul University Hospital-Sousse, Tunisia. Afr Health Sci 2019;19:2008–20.
- 34. Al-Zalabani A, AlThobyane OA, Alshehri AH, Alrehaili AO, Namankani MO, Aljafri OH. Prevalence of *klebsiella pneumoniae* antibiotic resistance in Medina, Saudi Arabia, 2014–2018. Cureus 2020;12:e9714.
- Oliveira R, Castro J, Silva S, Oliveira H, Saavedra MJ, Azevedo NF, et al. Exploring the antibiotic resistance profile of clinical *klebsiella pneumoniae* isolates in Portugal. Antibiotics (Basel) 2022;11:1613.
- Uzairue LI, Rabaan AA, Adewumi FA, Okolie OJ, Folorunso JB, Bakhrebah MA, et al. Global prevalence of colistin resistance in *klebsiella pneumoniae* from bloodstream infection: a systematic review and meta–analysis. Pathogens 2022;11:1092.
- Chiu SK, Ma L, Chan MC, Lin YT, Fung CP, Wu TL, et al. Carbapenem nonsusceptible *klebsiella pneumoniae* in Taiwan: dissemination and increasing resistance of carbapenemase producers during 2012–2015. Sci Rep 2018;8:8468.

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- Okanda T, Haque A, Koshikawa T, Islam A, Huda Q, Takemura H, et al. Characteristics of carbapenemase-producing *klebsiella pneumoniae* isolated in the intensive care unit of the largest tertiary hospital in Bangladesh. Front Microbiol 2020;11:612020.
- Hu F, Lin ML, Mou JL, Feng JH, Huang K, Lao YJ, et al. Molecular and clinical characteristics of carbapenem-resistant *klebsiella pneumoniae* isolates at a tertiary hospital in Wuhan, China. Infect Drug Resist 2023;16:65–76.