

## Prevalence and Antibiotic Resistance Profiles of Carbapenem-Resistant *Klebsiella Pneumoniae* Isolated from Tertiary Care Hospital, Egypt

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### ABSTRACT

**Background:** Carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) dissemination is a major healthcare problem due to its limited treatment options.

**Objective:** This study aimed to determine the prevalence and antimicrobial resistance profile of hospital infections caused by CR-Kp in Al-Ahrar Teaching Hospital. The study was conducted through the period from January 1, 2021 to December 31, 2021.

**Patients and Methods:** 650 clinical samples were collected from different ICU departments. *Klebsiella pneumoniae* isolates were identified by conventional methods. Susceptibility to carbapenems and other antibiotics was determined by disk diffusion method.

**Results:** Out of 650 clinical specimens, 142 *K. pneumoniae* were isolated with an isolation rate of 21.8%. *K. pneumoniae* showed that the majority (60.6%) of isolates were extensively-drug resistant (XDR), while 30.3% were multidrug resistant (MDR) and only 9.2% were susceptible. By disk diffusion method, the incidence of CR-Kp was 25.4% (36/142). Antibiotic susceptibility test showed that 100% of CR-Kp isolates were resistant to Amoxicillin/Clavulanic acid, Ampicillin/Sulbactam, Piperacillin/Tazobactam, cefepime, ceftriaxone, cefotaxime, ceftazidime and nitrofurantoin. High rate of resistance was also evident to aztreonam, norfloxacin (88.9%, for each) and amikacin (61.1%). Levofloxacin owned the lowest resistance rate (30.6%), followed by ciprofloxacin (44.4%) and gentamycin (47.2%). Antibiotic resistance pattern of isolated CR-Kp showed that the majority of the isolates (97.2%) were XDR, while only 2.8% were MDR.

**Conclusion:** About quarter of *K. pneumoniae* isolates were carbapenem-resistant with predominance of XDR isolates which represents a warning sign for which application of antibiotic stewardship is mandatory as well as strict infection control policies for prevention of development of pan-drug resistant bacteria.

**Keywords:** *Klebsiella pneumoniae*, Carbapenem resistance, Multidrug resistance, Extensively-drug resistant, Hospital acquired infection.

### INTRODUCTION

After *Streptococcus pneumoniae* (22.5%) and *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* has been recognised as the third main cause of Hospital Acquired Infections (HAIs) in Egypt (16.7%) (21.5%) respectively. In immunocompromised people, *K. pneumoniae* causes dangerous infections such as pneumonia, urinary tract infections, and bloodstream infections <sup>(1)</sup>.

Carbapenems are antibiotics with a broad spectrum of activity against Gram-negative and Gram-positive bacteria. They are administered as a last resort to infected individuals who are critically unwell or are suspected of possessing germs that are resistant to antibiotics <sup>(2)</sup>. Resistance to carbapenems in *K. pneumoniae* is primarily due to the production of carbapenemase enzymes or, in rare cases, to the production of extended-spectrum  $\beta$ -lactamase (ES $\beta$ L) and/or AmpC cephalosporinases combined with decreased permeability of the outer membrane due to loss or mutations in porins <sup>(3)</sup>. Rapid diagnosis of carbapenem-resistant *Enterobacteriales* is critical for infection management, patient treatment success, and carbapenem effectiveness maintenance <sup>(4)</sup>. Hence, this study was conducted to determine the prevalence and antimicrobial resistance profile of carbapenem resistant *K. pneumoniae* isolates.

### PATIENTS AND METHODS

This cross-sectional study was carried out over one year at the Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University in collaboration with ICU Departments in Al-Ahrar Teaching Hospital.

**Inclusion criteria:** Patients showing clinical criteria of nosocomial infections that developed at least 48-72 hours after admission including ventilator association pneumonia (VAP), urinary tract infection (UTI), surgical site infection (SSI), septicemia and chest infection.

**Exclusion criteria:** Patients with community acquired infection, patients had positive cultures for more than two bacterial species, or patients who were receiving antibiotic treatment were excluded.

Demographic data (age, sex, etc.) and clinical data (cause of admission, devices, antibiotic administration) were collected from all patients. Medical history of comorbidities; diabetes, hypertension, renal insufficiency, etc. and length of hospitalization were reported for each patient.

### Microbiological work up:

- **Clinical samples collection:** 650 non-duplicate clinical samples were aseptically collected from

patients who were admitted to ICU departments of Al-Ahrar Teaching Hospital in Zagazig, Egypt. Samples included endotracheal aspirates, sputa, urine, surgical site specimens and blood.

- **Cultivation and identification of *K. pneumoniae*:** Samples were collected and processed using standard microbiologic procedures<sup>(5)</sup>. All isolates in this study were cultured on MacConkey and nutrient agar media (Oxoid, UK), all plates were incubated aerobically at 35-37 °C for 24 hours and then examined for bacterial growth. Mucoid lactose fermenting pink colonies on MacConkey agar were subjected to identification as *K. pneumoniae* by Gram staining and conventional tests<sup>(6)</sup>.
- **Antibiotic susceptibility test:** Antibiotic susceptibility test (AST) was performed for the isolated *K. pneumoniae* by disk diffusion method on Muller Hinton agar (Oxoid, UK) according to clinical and laboratory standards institute (CLSI) 2021 guidelines. *K. Pneumonia* isolates with meropenem and/or imipenem zone diameter of less than 22 mm were reported as carbapenem resistant<sup>(7)</sup>.

The antibiotic discs (Bioanalysis®, Turkey) used for AST were: amoxicillin/clavulanic acid (AMC) 20/10 µg, ampicillin/sulbactam (SAM) 10/10 µg, piperacillin/tazobactam (TZP) 100/10 µg, ceftriaxone (CRO) 30 µg, cefotaxime (CTX) 30 µg, ceftazidime (CAZ) 30 µg, cefoxitin (FOX) 30 µg, cefipime (FEP) 30 µg, aztreonam (ATM) 30 µg, meropenem (MEM) 10 µg, imipenem (IPM) 100 µg, gentamicin (CN) 10 µg, amikacin (AK) 30 µg, levofloxacin (LEV) 5 µg, ciprofloxacin (CIP) 5 µg, norfloxacin (NOR) 10 µg and nitrofurantoin (F) 30 µg.

Multidrug resistant (MDR) bacteria were considered if the bacterial isolate was non-susceptible to at least one agent in three or more antimicrobial categories. The isolate was considered extensively drug resistant (XDR) if it was non-susceptible to at least one agent in all but two or fewer antimicrobial categories. Pan drug resistant (PDR) was defined as non-susceptible to all agents in all antimicrobial categories<sup>(8)</sup>.

- **Quality Control:** Quality control of the culture media, Gram stain and AST was checked using standardized reference strains *Klebsiella pneumoniae* ATCC 2146 and *Klebsiella pneumoniae* ATCC 1705 as positive controls (Liofilchem, Italy).

**Ethical consent:**

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

**Statistical analysis**

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ( $\chi^2$ ) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

**RESULTS**

**Sample processing and bacterial isolation:**

During the study period, 1282 cases were admitted to different ICU departments; 650 clinical samples (50.7%) had positive culture results with the majority of pathogens isolated from sputum samples (41.4%), followed by blood (32%), urine (18%) and pus samples (7.4%), while the least percentage of isolates were recovered from surgical site swabs (1.2%).

*K. pneumoniae* was the most predominant organism isolated from different clinical samples with an incidence rate of 21.8% (142/650) as shown in table (1). The majority of *K. pneumoniae* were isolated from Adult ICU (59.1%), followed by pediatric ICU (PICU) (26.8%), neonatal ICU (NICU) (10.6%) and surgical ICU (SICU) (3.5%).

**Table (1):** Microbiological profile of the microorganisms isolated from different samples

Organism	Total n=650	
	n	%
<i>K. pneumoniae</i>	142	21.8%
<i>Staph. Epidermidis</i>	129	19.8%
<i>Pseudomonas spp.</i>	76	11.7%
<i>Enterobacter spp.</i>	75	11.5%
<i>E. coli</i>	67	10.3%
<i>Candida spp.</i>	52	8.0%
<i>Staph. Aureus</i>	36	5.5%
<i>Citrobacter</i>	27	4.2%
<i>Enterococci</i>	19	2.9%
<i>Proteus Spp.</i>	14	2.2%
<i>Acenitobacter Spp.</i>	10	1.5%
<i>Strept. pneumoniae</i>	2	0.3%
<i>Serratia Spp.</i>	1	0.2%

There was a significant difference between specimen types regarding *K. pneumoniae* isolation showing that the majority of *K. pneumoniae* were isolated from sputum cultures (52.8%), followed by blood cultures (34.5%), urine cultures (9.2%) and pus cultures (2.1%), while the least percentage of isolates

were recovered from surgical site swabs (1.4%) as shown in table (2).

**Table (2):** Distribution of isolated *K. pneumoniae* among different samples

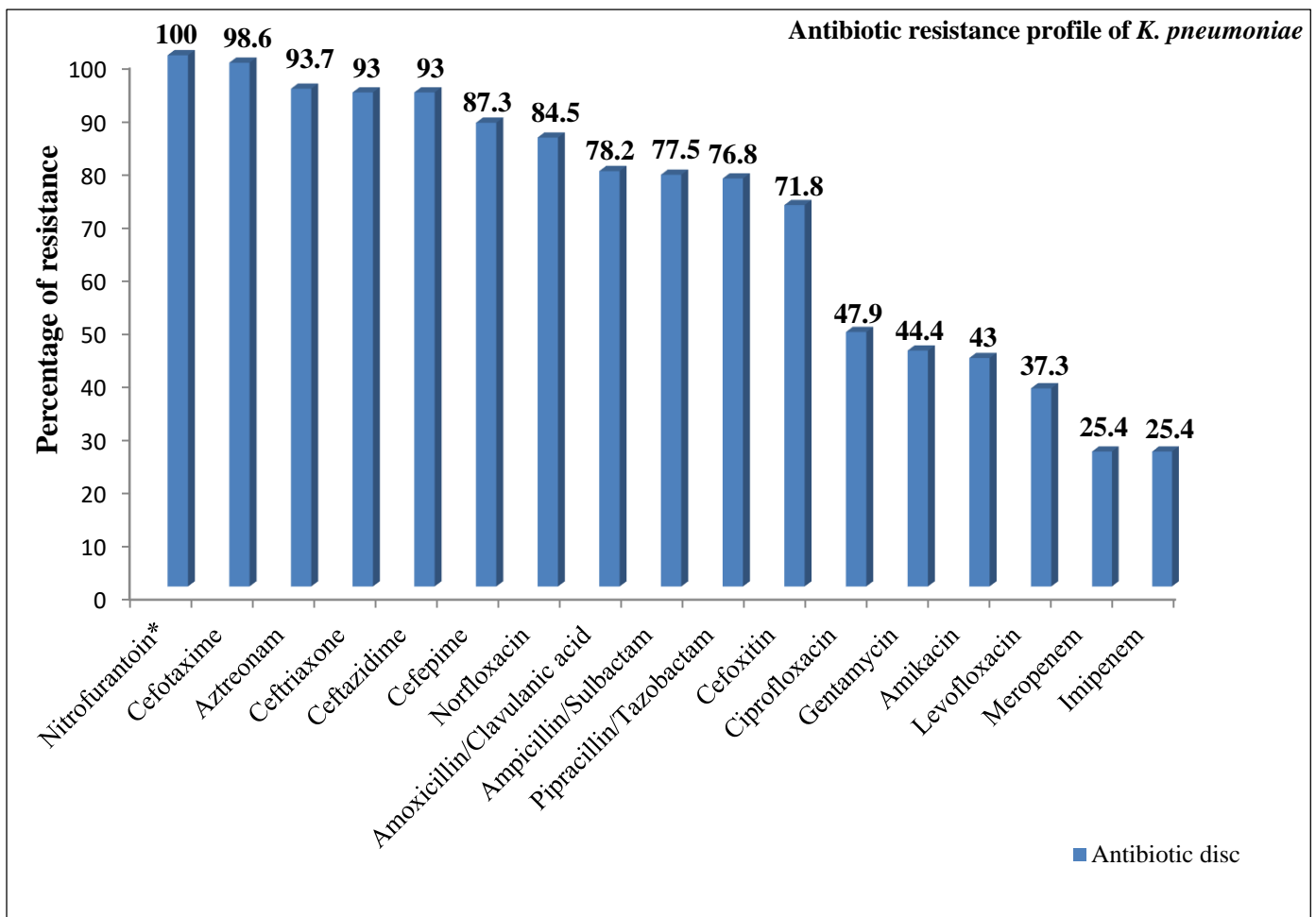
Specimen type	No. of isolates n=142	%	X <sup>2</sup>	P-Value
Sputum	75	52.8	105.971	0.000*
Blood	49	34.5		
Urine	13	9.2		
PUS	3	2.1		
Surgical site swab	2	1.4		

\* Significant difference (P < 0.05, by chi-square test)

**Antibiotic susceptibility test of *K. pneumoniae* isolates:**

In our study, *K. pneumoniae* isolates showed resistance to most types of antibiotics. The isolates showed the highest resistance rate to cefotaxime (98.6%), aztreonam (93.7%), ceftriaxone and ceftazidime (93% for each), while imipenem and meropenem owned the lowest resistance rates (25.4% for each). Antibiotic resistance profile has been presented in figure (1). The antimicrobial resistance patterns for the 142 isolates of *K. pneumoniae* was as follow; XDR (n=86, 60.6%), MDR (n=43, 30.3%), and susceptible *Klebsiella* (n= 13, 9.2%) strains were detected.

\*Used only with urine samples



**Figure (1):** Antibiotic resistance profile of *K. pneumoniae* isolates by disk diffusion method

**Antibiotic susceptibility test of carbapenem-resistant *K. pneumoniae* isolates:**

The prevalence of CR-Kp was 25.4% (36/142) detected by using disk diffusion test. The majority of CR-Kp isolates were recovered from sputum specimens (36.1%), followed by blood (27.8%), urine (25%) and surgical site swabs and pus (5.6%) for each (Table 3). The most common source of CR-Kp isolates came from adult ICU (61.1%), followed by PICU and NICU (13.9%) for each). On the other hand, 11.1% of CR-Kp isolates were recovered from SICU.

**Table (3):** Incidence and distribution of carbapenem-resistant *K. pneumoniae* (CR-Kp) among different samples

Specimen type	No. of CR-Kp out of 142 <i>K. pneumoniae</i> isolates	%	X <sup>2</sup>	P-Value
sputum	13	36.1	32.968	0.0009*
blood	10	27.8		
urine	9	25.0		
pus	2	5.6		
Surgical site swab	2	5.6		
<b>Total</b>	<b>36</b>	<b>25.4</b>		

\* Significant difference (P < 0.05, by chi-square test), X<sup>2</sup>: Chi-square test.

The majority of studied patients infected with CR-Kp were males (58.3%) and the mean age was 36.86 ± 23.51 years. The most common reason for admission was poly-trauma (22.1%), followed by respiratory distress (13.9%) as shown in table (4).

**Table (4):** Demographic and clinical data of our studied cases with CR-Kp infections

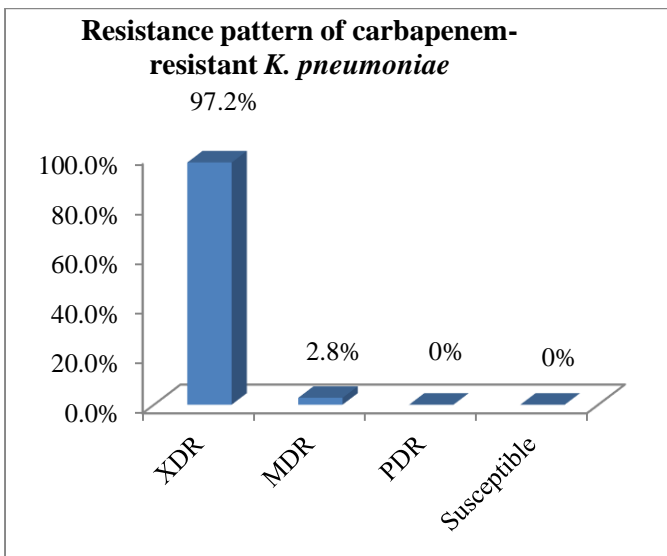
Variable	n=36 (%)
<b>Age</b>	
Range (years)	0 – 80
Mean ± SD*	36.86 ± 23.51
<b>Sex (male/female)</b>	21/15 (58.3/41.7)
<b>Cause of admission</b>	
Poly-trauma	8 (22.1)
Respiratory distress	5 (13.9)
DKA	4 (11.1)
Heart failure	4 (11.1)
Surgical infection	4 (11.1)
Intracranial hemorrhage	3 (8.3)
Pulmonary edema	2 (5.6)
Renal failure	2 (5.6)
COPD	1 (2.8)
Pulmonary embolism	1 (2.8)
Respiratory failure	1 (2.8)
Status asthmaticus	1 (2.8)

Hypertension and diabetes mellitus were the most common co-morbidities among our studied patients (33.3% and 30.6%, respectively). Mechanical ventilation and urinary catheterization represented the highest incidence (86.1%, for each) of risk factors associated with CR-Kp infections. Most of the patients (61.1%) had long hospital stay (≥ 7 days) (Table 5).

**Table (5):** Risk factors associated with infection by carbapenem-resistant *K. pneumoniae*

Variable	n (%)
<b>Associated co-morbidities</b>	
Hypertension	12 (33.3)
Diabetes mellitus	11 (30.6)
Heart failure	8 (22.2)
Recent surgery	6 (16.7)
Renal insufficiency	5 (13.9)
Prematurity	4 (11.1)
Congenital anomaly	2 (5.6)
Malignancy	2 (5.6)
<b>Devices</b>	
Mechanical ventilation	31 (86.1)
Urinary catheterization	31 (86.1)
Central venous catheterization	16 (44.4)
<b>Period of ICU admission</b>	
Less than 1 week	14 (38.9)
More than 1 week	22 (61.1)

Carbapenem resistant *K. pneumoniae* isolates showed 100% resistance to amoxicillin/clavulanic acid, ampicillin/sulbactam, piperacillin/tazobactam, cefepime, ceftriaxone, cefotaxime, ceftazidime and nitrofurantoin. High rate of resistance was also evident to aztreonam, norfloxacin (88.9%, for each) and amikacin (61.1%). Levofloxacin owned the lowest resistance rate (30.6%), followed by ciprofloxacin (44.4%) and gentamycin (47.2%). Antibiotic resistance pattern of isolated carbapenem resistant *K. pneumoniae* showed that the majority of the isolates (97.2%) were XDR, while only 2.8% were MDR as shown in figure (2).



**Figure (2):** Resistance pattern of carbapenem-resistant *K. pneumoniae*

## DISCUSSION

*K. pneumoniae* isolates that are multidrug resistant (MDR) have developed resistance to four different antibiotic classes: third-generation cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems<sup>(9)</sup>. The emergence of carbapenem resistance is gaining considerable attention because carbapenems represent antibiotics of last resort for severe infections caused by MDR strains<sup>(10)</sup>.

During our study, the highest number of pathogens were isolated from sputum cultures (41.4%), followed by blood cultures (32%) and urine cultures (18%). This is in agreement with a study by **Kumar et al.**<sup>(11)</sup> who reported that sputum specimens were the most common source of pathogens, unlike the results of a study done by **Khalifa et al.**<sup>(10)</sup> who reported higher recovery from blood specimens (39%) in comparison with respiratory specimens (18%). This variation in results could be justified by the difference in the included subjects in both studies. In our study all included specimens were collected from ICU patients where the risk of respiratory-device associated infections are high, while the other study included patients only from wards where respiratory device use would most probably be less frequent.

Our study showed that *K. pneumoniae* was the most predominant organism isolated from different clinical samples with an incidence rate of 21.8%. This result is coincident with that of **Negm et al.**<sup>(12)</sup> who reported that *K. pneumoniae* was the most frequently identified pathogen (33.5%) among different clinical samples isolated from ICU departments in Zagazig University Hospitals. In the same locality, a study done by **Morsi**<sup>(13)</sup> detected similar incidence (23.3%) of *K. pneumoniae* isolated from different clinical samples. In Kafrelsheikh city, Egypt, *K. pneumoniae* represented (22.8%)<sup>(14)</sup>. Also, a study by **Balakrishnan et al.**<sup>(15)</sup>, at different ICUs of a tertiary care teaching hospital, India, reported that *K. pneumoniae* was the most common isolated pathogen with an incidence rate (25.8%),

followed by *Acinetobacter* spp. (23.4%). However, in an Egyptian hospital in Cairo, **Shebl et al.**<sup>(16)</sup> reported that *E. coli* was the most frequently isolated pathogen (30.7%) followed by *Staph. aureus* (21.1%), while *Klebsiella* species accounted for 20.9% in their study. Also, a study by **Metri and Jyothi**<sup>(17)</sup> at different ICU departments in an Indian Hospital reported that *E. coli* represented the most frequently isolated organism (22.8%) followed by *Klebsiella* species (16.8%).

*K. pneumoniae* typically colonizes human mucosal surfaces of the oropharynx and gastrointestinal tract; therefore it is regarded as the most common cause of hospital-acquired pneumonia in the United States<sup>(18)</sup>. Our study revealed that there was a significant difference between specimen types regarding *K. pneumoniae* isolation, showing that the majority of *K. pneumoniae* isolates were recovered from respiratory specimens (52.8%). This finding is similar to a study by **Wang et al.**<sup>(19)</sup> who reported that the respiratory tract was the most common site of *K. pneumoniae* infection in the Republic of China. Also, a study by **Kumar et al.**<sup>(11)</sup> reported that sputum samples were the most common source of *Klebsiella* spp. isolation. However, **Rabie and Abdallah**<sup>(20)</sup> who collected samples from Zagazig University Hospitals, Egypt reported that *K. pneumoniae* samples were mainly isolated from urine specimens (33.3%), followed by blood (27.9%), sputa and surgical wound (19.4%, for each). Also in the same locality, a study by **Morsi**<sup>(13)</sup> reported that urine specimens were the most common source of *K. pneumoniae* isolation.

Regarding antibiotic susceptibility test, our study revealed that *K. pneumoniae* isolates from urine samples showed 100% resistance with nitrofurantoin, which is similar to the result by **Shanmugam et al.**<sup>(21)</sup>. Also, *K. pneumoniae* isolates showed the highest resistance to 3<sup>rd</sup> generation cephalosporins (including cefotaxime, ceftriaxone and ceftazidime) and aztreonam with a resistance range (93% - 98.6%). This agrees with results reported by **Aamir et al.**<sup>(22)</sup> in Zagazig University Hospitals, who revealed that the highest antibiotic resistance among *K. pneumoniae* isolates was with 3<sup>rd</sup> generation cephalosporins and aztreonam (92% for each). Previous studies in Egypt and other countries reported similar results<sup>(12, 23)</sup>. The high resistance to 3<sup>rd</sup> generation cephalosporins might be due to the excess consumption of these antibiotics as empirical treatment of nosocomial infections in Egyptian hospitals.

High resistance rate was also evident to cefoxitin and 4<sup>th</sup> generation cephalosporins (cefepime) with resistance rate (71.8% and 87.3%, respectively). Higher resistance levels were detected by **Aamir et al.**<sup>(22)</sup> who reported resistance rates of 92% and 90%, respectively.

Resistance to  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination such as piperacillin-tazobactam, ampicillin-sulbactam and amoxicillin-clavulanic acid was relatively high with a resistance range (76.8% - 78.2%). On the other hand, a study by **Morsi**<sup>(13)</sup> detected lower

resistance rate with piperacillin-tazobactam (27%), while high resistance rate was observed with amoxicillin-clavulanic acid (88%). Also, **Nirwati et al.** <sup>(24)</sup> reported good susceptibility to both piperacillin-tazobactam and amoxicillin-clavulanic acid with only resistance rate of 10.5% and 36.7%, respectively. The variety of results among researchers may be due to the fact that the spectrum of activity of these  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations covers mainly class A (with the exception of KPC) and some class C serine  $\beta$ -lactamases <sup>(25)</sup>. Also, the emergence of inhibitor-resistant TEM variants with lowered susceptibility to clavulanic acid, sulbactam, and tazobactam has been documented <sup>(26)</sup>.

However, our results revealed that imipenem and meropenem owned the lowest resistance rates (25.4% for each), followed by levofloxacin (37.3%), amikacin (43%), gentamycin (44.4%) and ciprofloxacin (47.9%). These results are highly compatible with the results reported by **Aamir et al.** <sup>(22)</sup> with higher resistance rate reported with amikacin and gentamycin (60% and 70%, respectively). Also, **Nirwati et al.** <sup>(24)</sup> reported close levels of resistance with much lower resistance rates with meropenem and amikacin (1.2% and 4.8%, respectively). The variety in the resistance levels to imipenem and meropenem may be due to the proper selection of cases for carbapenem treatment, which keep the sensitivity of these drugs.

Our study showed that 25.4% (36/142) of *K. pneumoniae* were carbapenem resistant. This result is well matching with **Morsi** <sup>(13)</sup> who reported that 25% of *K. pneumoniae* isolates were carbapenemase producers. In the same locality, **Aamir et al.** <sup>(22)</sup> detected a higher incidence (32%) of CR-Kp. The high frequency of CR-Kp could be attributed to the excessive empirical use of carbapenems and the improper application of the infection control measures.

The antimicrobial resistant pattern for *K. pneumoniae* isolates showed that most of the isolates were XDR (60.6%) and 30.3% were MDR, while 9.2% were susceptible. These results are comparable to a study carried out in Minia, Egypt by **Hassuna et al.** <sup>(27)</sup> who reported an alarming occurrence of XDR *K. pneumoniae* with an incidence of 83.3%. Different figures were shown in a study done by **Aamir et al.** <sup>(22)</sup> who reported that 47.2% were MDR and 36.1% were XDR. A higher incidence of MDR *K. pneumoniae* was detected in a study by **Wasfi et al.** <sup>(28)</sup> who reported 77.7% MDR *K. pneumoniae*. Many factors may contribute to the spread of MDR and XDR isolates such as limited adherence to infection control protocols and unnecessary use of antimicrobials.

Among our studied cases, it was observed that there was a significant difference between specimen types regarding CR-Kp isolation, showing that the majority of CR-Kp was isolated from sputum specimens (36.1%). This is in agreement with **Radhika and Padmaja** <sup>(29)</sup> who reported that the major source of CR-Kp was sputum samples. The majority of CR-Kp in

sputum specimens in our study may be associated with the reason that most of the patients were on mechanical ventilation that plays a key role in the transmission of resistant bacterial strains <sup>(30)</sup>. However, urine and blood were the major source of CR-Kp in other studies <sup>(14, 10)</sup>.

The most common source of CR-Kp isolates in our study came from adult ICU (61.1%), followed by PICU and NICU (13.9%, for each) and the least percentage of isolates came from SICU (11.1%). According to **Perez and Van Duin** <sup>(31)</sup>, persons commonly infected by CR-Kp are elderly having several comorbidities and have been subjected to invasive procedures. Furthermore, they are frequently severely ill and require intensive care.

Regarding antibiotic susceptibility test, CR-Kp isolates showed 100% resistance to amoxicillin/clavulanic acid, ampicillin/sulbactam, piperacillin/tazobactam, cefepime, ceftriaxone, cefotaxime, cefoxitin, ceftazidime and nitrofurantoin. High rate of resistance was also evident to aztreonam, norfloxacin (88.9%, for each) and amikacin (61.1%). Levofloxacin owned the lowest resistance rate (30.6%), followed by ciprofloxacin (44.4%) and gentamycin (47.2%). This finding is in accordance with **Morsi** <sup>(13)</sup> except for cefepime, amoxicillin/clavulanic acid and piperacillin/tazobactam (95.2%, 88.1% and 35.7%, respectively).

Also, antibiotic susceptibility test results of CR-Kp isolates showed a high incidence of XDR profile (97.2%), while only 2.8% of isolates were MDR and no PDR isolates were detected. In line with our data, **Ramsamy et al.** <sup>(32)</sup> reported that all CR-Kp isolates were XDR. In china, **Bi et al.** <sup>(33)</sup> reported that the dissemination of clinical XDR *K. pneumoniae* strains result from horizontal transmission of multiple resistance determinants via plasmids. The fact that nosocomial infections with XDR *K. pneumoniae* are associated with delays in proper therapy is becoming a rising global reality, offering severe challenges to clinically effective therapeutic alternatives across the world. The rising incidence and global spread of these clinical XDR strains endangers public health <sup>(34)</sup>. Different figures were reported in other studies in Egypt and other countries reporting high incidence of MDR CP-Kp <sup>(14, 24)</sup>. Variety in antibiotic resistance pattern among studies may be attributed to different infections and specimen types, patient's risk factors, site of patient admission and infection control measures <sup>(35)</sup>.

In our study, the most common cause of admission was poly-trauma (22.1%), followed by respiratory distress (13.8%). Several studies supported that ICU stay was associated with CR-Kp infection as the contact and airborne transmission of these resistant bacteria in ICU environment undoubtedly led to nosocomial infection particularly among critically ill patients with prolonged ICU stay, invasive procedures and those under broad-spectrum antibiotics who are at increased risk of CR-Kp infection <sup>(31)</sup>.

Our study showed that hypertension and diabetes mellitus were the most common co-morbidities associated with CR-Kp infections (33.3% and 30.6%, respectively). The use of mechanical ventilation, urinary catheter and central venous catheter were the most common risk factors associated with CR-Kp infections. Results regarding the previous associations are alike with those observed by **Bi et al.** (33) in China, which showed that central venous catheter, mechanical ventilation and prolonged hospitalization prior to culture were identified as independent risk factors for carbapenem-non-susceptible *K. pneumoniae*.

## CONCLUSION

Our study concluded that carbapenem resistant *K. pneumoniae* in Al-Ahrar Teaching Hospital is an increasing problem caused by the selective pressure exerted by intensively used carbapenems. This requires more attention to rationalize the antibiotic usage and strengthen the application of infection control precautions. It is very important to detect and report carbapenem resistance as it would improve clinical consequences by optimizing the selection and beginning of appropriate antibiotic therapy in a timely manner.

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**Author contribution:** Authors contributed equally in the study.

## REFERENCES

1. **Shebl E, Said A, El-Korashi L et al. (2019):** The outcome of hospital-acquired pneumonia in patients admitted for long-term care according to the antibiotic duration. The Egyptian Journal of Chest Diseases and Tuberculosis, 68 (3): 378-82.
2. **Osei Sekyere J, Reta M, Bernard Fourie P (2021):** Risk factors for, and molecular epidemiology and clinical outcomes of, carbapenem-and polymyxin-resistant Gram-negative bacterial infections in pregnant women, infants, and toddlers: a systematic review and meta-analyses. Annals of the New York Academy of Sciences, 1502 (1): 54-71.
3. **Sabtcheva S, Todorova B, Ivanov I et al. (2016):** Comparison of two combination disc tests for phenotypic detection of carbapenemase-producing Enterobacteriaceae. Probl Inf Parasit Dis., 44: 8-11.
4. **Hara G, Gould I, Endimiani A et al. (2013):** Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: recommendations from an International Working Group. Journal of Chemotherapy, 25 (3): 129-40.
5. **Garrity G, Bernner D, Krig N (2005):** Stalery, editors. Bergey's manual of systematic bacteriology. 2nd Volume: New York: Springer., Pp: 505-536. <https://scirp.org/reference/referencespapers.aspx?referenceid=42923>
6. **Forbes B, Sahn D, Weissfeld A (2007):** Bailey and Scott's Diagnostic Microbiology. 12th Edition, Mosby Elsevier, China, Pp: 842-855. [https://www.scirp.org/\(S\(i43dyn45teexjx455q3d2q\)\)/reference/ReferencesPapers.aspx?ReferenceID=1418907](https://www.scirp.org/(S(i43dyn45teexjx455q3d2q))/reference/ReferencesPapers.aspx?ReferenceID=1418907)
7. **CLSI (2021):** Performance standards for antimicrobial susceptibility testing. 31<sup>st</sup> ed. Weinstein M, Lewis II J, Bobenchik A, Campeau S, Cullen S, Galas M, et al., editors: CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute, Pp: 1-13. [https://clsi.org/media/3481/m100ed30\\_sample.pdf](https://clsi.org/media/3481/m100ed30_sample.pdf)
8. **Basak S, Singh P, Rajurkar M (2016):** Multidrug resistant and extensively drug resistant bacteria: a study. Journal of Pathogens, 16: 4065603.
9. **Navon-Venezia S, Kondratyeva K, Carattoli A (2017):** Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance. FEMS Microbiology Reviews, 41 (3): 252-75.
10. **Khalifa H, Soliman A, Ahmed A et al. (2017):** High carbapenem resistance in clinical gram-negative pathogens isolated in Egypt. Microbial Drug Resistance, 23 (7): 838-44.
11. **Kumar N, Singh V, Beniwal V (2019):** Modified combined disc test (mCDT): a novel, labor-saving and 4 times cheaper method to differentiate Class A, B and D carbapenemase-producing Klebsiella species. Diagnostic Microbiology and Infectious Disease, 93 (2): 96-100.
12. **Negm E, Mowafy S, Mohammed A et al. (2021):** Antibiograms of intensive care units at an Egyptian tertiary care hospital. The Egyptian Journal of Bronchology, 15 (1): 1-15.
13. **Morsi S (2016):** Comparative evaluation of phenotypic and genotypic methods for detection of carbapenemases in clinically significant Klebsiella pneumoniae Isolates. The Egyptian Journal of Medical Microbiology (EJMM), 25 (1): 109-116.
14. **El-Domany R, El-Banna T, Sonbol F et al. (2021):** Co-existence of NDM-1 and OXA-48 genes in Carbapenem Resistant Klebsiella pneumoniae clinical isolates in Kafrelsheikh, Egypt. African Health Sciences, 21 (2): 489-96.
15. **Balakrishnan S, Shaji N, Jakribettu R et al. (2019):** Antibiotic resistance pattern of gram negative bacterial isolates from the clinical samples from critical care units of a tertiary care centre. Int J Med Lab Res., 4 (1): 17-22.
16. **Shebl R, Mosaad Y (2019):** Frequency and antimicrobial resistance pattern among bacterial clinical isolates recovered from different specimens in Egypt. Cent African J Public Heal., 5 (1): 36-45.
17. **Metri B, Jyothi Z (2018):** Bacteriological profile of gram negative nosocomial isolates from intensive care units and their antibiogram in a tertiary care hospital of South India. International Journal of Medical Microbiology and Tropical Diseases, 4 (4): 243-250.
18. **Ashurst JV, Dawson A (2021):** Klebsiella pneumonia. StatPearls. <https://www.ncbi.nlm.nih.gov/books/NBK519004/>



19. Wang C, Yuan Z, Huang W *et al.* (2019): Epidemiologic analysis and control strategy of *Klebsiella pneumoniae* infection in intensive care units in a teaching hospital of People's Republic of China. *Infection and Drug Resistance*, 12: 391-96.
20. Rabie R, Abdallah A (2019): Plasmid mediated colistin resistant genes *mcr-1* and *mcr-2* among *Escherichia coli* and *Klebsiella pneumoniae* isolates at Zagazig University hospitals, Egypt. *Internal Medicine*, 14: 5-9.
21. Shanmugam P, Meenakshisundaram J, Jayaraman P (2013): *blaKPC* gene detection in clinical isolates of carbapenem resistant Enterobacteriaceae in a tertiary care hospital. *Journal of Clinical and Diagnostic Research*, 7 (12): 2736-42.
22. Aamir R, Ateya R, Yahia S (2021): Ceftazidime/Avibactam Efficiency tested In Vitro against Carbapenem-resistant *Klebsiella pneumoniae* isolated from Neonates with Sepsis. *Microbes and Infectious Diseases*, 18: 529-540.
23. Ugrakli S, Dogan M (2020): Growing Threat Increased Carbapenem-Resistance among *Klebsiella pneumoniae*; Antibiotic Susceptibility Pattern of *Klebsiella pneumoniae* in a Tertiary Care Hospital. *International Journal of Clinical Microbiology*, 1 (2): 1-7.
24. Nirwati H, Sinanjung K, Fahrnunissa F *et al.* (2019): Biofilm formation and antibiotic resistance of *Klebsiella pneumoniae* isolated from clinical samples in a tertiary care hospital, Klaten, Indonesia. *BMC Proceedings*, 13 (11): 1-8.
25. Tehrani K, Martin N (2018):  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations: an update. *Medchemcomm*, 9 (9): 1439-56.
26. Chaibi E, Sirot D, Paul G *et al.* (1999): Inhibitor-resistant TEM  $\beta$ -lactamases: phenotypic, genetic and biochemical characteristics. *Journal of Antimicrobial Chemotherapy*, 43 (4): 447-58.
27. Hassuna N, AbdelAziz R, Zakaria A *et al.* (2020): Extensively-drug resistant *Klebsiella pneumoniae* recovered from neonatal sepsis cases from a major NICU in Egypt. *Frontiers in Microbiology*, 11: 1375-79.
28. Wasfi R, Elkhatib W, Ashour H (2016): Molecular typing and virulence analysis of multidrug resistant *Klebsiella pneumoniae* clinical isolates recovered from Egyptian hospitals. *Scientific Reports*, 6 (1): 1-11.
29. Radhika B, Padmaja J (2015): Detection of serine carbapenemase and metallo carbapenemase enzymes in *Klebsiella pneumoniae* in a tertiary care hospital. *Am J Sci Med Res.*, 1: 136-47.
30. Medell M, Medell M, Martínez A *et al.* (2012): Characterization and sensitivity to antibiotics of bacteria isolated from the lower respiratory tract of ventilated patients hospitalized in intensive care units. *The Brazilian Journal of Infectious Diseases*, 16 (1): 45-51.
31. Perez F, Van Duin D (2013): Carbapenem-resistant Enterobacteriaceae: a menace to our most vulnerable patients. *Cleveland Clinic Journal of Medicine*, 80 (4): 225-29.
32. Ramsamy Y, Mlisana K, Allam M *et al.* (2020): Genomic analysis of carbapenemase-producing extensively drug-resistant *Klebsiella pneumoniae* isolates reveals the horizontal spread of *p18-43\_01* plasmid encoding *blaNDM-1* in South Africa. *Microorganisms*, 8 (1): 137-42.
33. Bi W, Liu H, Dunstan R *et al.* (2017): Extensively drug-resistant *Klebsiella pneumoniae* causing nosocomial bloodstream infections in China: molecular investigation of antibiotic resistance determinants, informing therapy, and clinical outcomes. *Frontiers in Microbiology*, 8:1230.
34. Zhao F, Zhang J, Fu Y *et al.* (2015): Dissemination of extensively drug-resistant and KPC-2 producing *Klebsiella pneumoniae* isolated from bloodstream infections. *The Journal of Infection in Developing Countries*, 9 (09): 1016-21.
35. Abdallah A, Mohammed H, El Maghraby H (2021): Expression of Mex AB-Opr M efflux pump system and meropenem resistance in *Pseudomonas aeruginosa* isolated from surgical intensive care unit. *Microbes and Infectious Diseases*, 2 (4): 781-9.