SURVEY ON THE RATE AND ANTIBIOTIC RESISTANCE OF *KLEBSIELLA PNEUMONIAE* IN PATIENTS TREATED AT TWO DEPARTMENTS - INTERNAL INTENSIVE CARE UNIT AND SURGICAL INTENSIVE CARE UNIT - MILITARY HOSPITAL 175

Nguyen Thi Trang[1], Le Thuy Duong[1], Tran Khanh Hoang[1], Nguyen Ngoc Đang Khoa[2], Pham Thi Huyen[1], Huynh Quoc Huy[1], Nguyen Thi Bich Thuy[l], Đinh Thi Ngan Ha[1]

ABSTRACT:

Background: Strains of K. pneumoniae that produce extended-spectrum β-lactamase (ESBL) and carbapenemases (CARB) are becoming more common and present a significant challenge in treating hospital-acquired infections, especially in Intensive Care Units (ICU).

Objectives: To describe the characteristics of K. pneumoniae infections and antibiotic resistance (phenotypic and genotypic) in patients treated at two departments: the Internal Intensive Care Unit (A12.1) and the Surgical Intensive Care Unit (A12.2) of Military Hospital 175.

Subjects and Methods: A retrospective study on 235 strains of K. pneumoniae isolated from clinical specimens of patients treated in Intensive Care Units (ICU).

Results: There were 157 strains of K. pneumoniae producing CARB (70.1%) and 79 strains (35.3%) producing ESBL and CARB. Among the 21 strains analyzed for drug

[1]Military Hospital 175
[2]Institute of Health, University of Wolverhampton
Corresponding author: Nguyen Thi Trang (drtrangbv175@gmail.com)
Receipt date: April 26[th], 2024 *Review date: May 06[th], 2024*
Accepted date: June 30[th], 2024

resistance genes: 6 strains (28.6%) carried one gene, 14 strains (66.7%) carried two genes, and especially, one strain carried 3 genes; NDM was the most commonly popular gene. The antibiotic resistance rates of K. pneumonia strains were high: Imipenem 65.4% - 77.4%, Meropenem 64.7% - 79.2%, Amikacin 24.1% - 56%, Ceftazidime-Avibactam 61.5% - 71.8%, and Colistin 9.3% - 44.7%.

Conclusions: The rates of K. pneumoniae-producing ESBL and CARB were relatively high. Strains isolated in the Internal Intensive Care Unit showed higher antibiotic resistance rates than those in the Surgical Intensive Care Unit (statistically significant difference with $p<0.05$ for Aminoglycosides and Colistin). However, the antibiotic resistance rates remained high in both departments, with a particularly rapid increase in resistance to Carbapenem, Colistin, and new antibiotics like Ceftazidime-Avibactam.

Keywords: Klebsiella pneumoniae, antibiotic resistance, Internal Intensive Care Unit, Surgical Intensive Care Unit.

I. INTRODUCTION

Antibiotic resistance has increasingly become a significant public health challenge globally, with nearly 5 million deaths and at least 1.27 million fatalities worldwide in 2019[1]. The antibiotic resistance in *K. pneumoniae* strains producing ESBL and CARB is increasingly concerning. Despite numerous studies that have been applied to sustain progress against antibiotic resistance, the incidence of ESBL- and CARB-producing *K. pneumoniae* infections is increasing significantly[2]. Patients treated in Intensive Care Units are at high risk for infections, particularly *K. pneumoniae*, which is often the reason that greatly affects the effectiveness and cost of treatment for patients[3].

Based on this situation, this study was conducted to describe the rates of *K. pneumoniae* infections and the characteristics of antibiotic resistance (phenotypic and genotypic) in patients treated in the Internal Intensive Care Unit and Surgical Intensive Care Units of the 175 Military Hospital. The results of this study are intended to support antibiotic selection in treating *K. pneumoniae* in patients in these Intensive Care Units.

II. SUBJECTS AND METHODS

1. Study Subjects

K. pneumoniae strains isolated from clinical specimens (such as respiratory samples, blood catheters, urine, pus, cerebrospinal fluid, etc.) of patients treated in the Internal Intensive Care Unit and Surgical Intensive Care Units.

2. Study Methods

Study design: Retrospective study

Duration: January 2023 – November 2023

Techniques & Statistics anaanalysis:

Clinical specimens collected from patients in the Internal and Surgical Intensive Care Units were processed using culturing techniques according to the Microbiology Lab procedures. Pathogenic *K. pneumoniae* strains were identified and assessed for antibiotic susceptibility using the BD Phoenix NMIC/ID-504 panel on the Phoenix BD M50 system by Becton Dickinson. The results for sensitivity, resistance, and intermediate reactions to antibiotics were interpreted following CLSI 2023 guidelines.

Some multidrug-resistant *K. pneumoniae* strains underwent additional real-time PCR with multiple primers to detect the presence of five carbapenem-resistance genes (OXA-48, KPC, VIM, IMP, NDM).

Data processing: Using IBM SPSS software version 20. P value <0.05 was considered statistically significant.

III. STUDY RESULTS

Table 1: Distribution rates of K. pneumoniae by clinical specimen

Specimen	Internal ICU	Surgical ICU	Total
Respiratory	114 (65.1%)	41 (68.3%)	155 (66.0%)
Blood - Catheter	48 (27.4%)	11 (18.3%)	59 (25.1%)
Fluid - Pus	4 (2.3%)	6 (10.0%)	10 (4.3%)
Urine	7 (4.0%)	1 (1.7%)	8 (3.4%)
Stool	2 (1.1%)	0 (0.0%)	2 (0.9%)
Cerebrospinal Fluid	0 (0.0%)	1 (1.7%)	1 (0.4%)
Total	175 (100.0%)	60 (100.0%)	235 (100.0%)

During the study period, 235 *K. pneumoniae* strains were isolated. 178 from male patients (75.7%) and 57 from female patients (24.3%); 175 strains (74.5%) from the A12.1 department and 60 strains (25.5%) from the A12.2 department. *K. pneumoniae* was most commonly isolated from respiratory specimens (66.0%) and secondarily from blood-catheter specimens (25.1%) (Table 1).

Table 2: The rate of K. pneumoniae producing CARB and ESBL

Department	CARB (+)		ESBL (+)		CARB + ESBL	
	Quantity	*Percentage (%)*	*Quantity*	*Percentage (%)*	*Quantity*	*Percentage (%)*
Internal ICU (n=170)	128	75.3	77	45.3	68	40.0
Surgical ICU (n=54)	29	53.7	20	37.0	11	20.4
p	**0.001**		0.111		**0.001**	

The rate of CARB-producing *K. pneumoniae* strains in A12.1 was 75.3%, higher than in A12.2 (53.7%), and this difference was statistically significant ($p<0.05$). Additionally, the rate of ESBL-producing strains was lower than that of CARB, with rates of 45.3% and 37% in A12.1 and A12.2, respectively. Among them, there were 79 *K. pneumoniae* strains produced CARB and ESBL, and this difference was also statistically significant ($p<0.05$) (Table 2).

Table 3: Rates of antibiotic resistance genes

Antibiotic Resistance Gene	NDM	OXA 48	KPC	IMP	VIM
Number of strains with gene (n=21)	17	16	3	1	0
Percentage (%)	80.9	76.2	14.3	4.7	0

The study showed that NDM and OXA 48 were the most common antibiotic resistance genes, with rates of 80.9% and 76.2%, respectively, KPC gene accounted for 14.3%, while the IMP gene was only 4.7% (Table 3).

Table 4: Rates of K. pneumoniae with antibiotic resistance genes

Number of Genes	Gene Type	Total Strains (n=21)	Percentage (%)
1	KPC	2	9.5
1	NDM	2	9.5
1	OXA 48	1	4.8
1	IMP	1	4.8
2	NDM + OXA 48	14	66.7
3	NDM + OXA 48 + KPC	1	4.8

The results of antibiotic resistance gene determination in 21 *K. pneumoniae* strains showed that the majority of strains (66.7%) carried two genes (NDM and OXA 48). Additionally, six strains had one gene (KPC: two strains, NDM: two strains, IMP: one strain, OXA 48: one strain), with one strain carrying all three resistance genes (NDM + OXA 48 + KPC) (Table 4).

Table 5: Antibiotic resistance rates of K. pneumoniae

Antibiotics	Internal ICU		Surgical ICU		p
	Quantity	Percentage (%)	Quantity	Percentage (%)	
Amikacin	94/168	56.0	13/54	24.1	**0.000**
Ampicillin	168/168	100.0	54/54	100.0	-
Ampicillin-Sulbactam	145/167	86.8	43/54	79.6	0.161
Cefazolin	141/166	84.9	42/53	79.2	0.313
Cefepime	138/168	82.1	41/54	75.9	0.315
Ceftazidime	142/168	84.5	42/54	77.8	0.323
Ceftazidime-Avibactam	117/163	71.8	32/52	61.5	0.214
Ceftriaxone	138/167	82.6	41/54	75.9	0.275
Ciprofloxacin	147/168	87.5	44/54	81.5	0.292
Colistin	71/170	44.7	5/54	9.3	**0.000**
Ertapenem	134/168	79.8	36/52	69.2	0.113
Gentamicin	119/168	70.8	27/54	50.0	**0.030**
Imipenem	130/168	77.4	34/52	65.4	0.051
Meropenem	133/168	79.2	33/51	64.7	0.051
Minocycline	58/83	69.9	21/32	65.6	0.659
Piperacillin-Tazobactam	131/167	78.4	37/54	68.5	0.182
Tigecycline	112/161	69.6	29/50	58.0	0.129
SXT	124/168	73.8	37/54	68.5	0.538

The results from Table 5 showed that the antibiotic resistance rates of *K. pneumoniae* to the Carbapenem group (Ertapenem – Imipenem – Meropenem) in A12.1 were 79.8%, 77.4%, and 79.2%, respectively, and in A12.2 were 69.2%, 65.4%, and 64.7%, respectively. The resistance rate to Amikacin in A12.1 was 56% and in A12.2 was 24.1%. The resistance rate to Colistin in A12.1 was 44.7% and in A12.2 was 9.3%. The resistance rate to Ceftazidime-Avibactam remained very high (71.8% in A12.1 and 61.5% in A12.2). These differences were statistically significant for the Aminoglycosides and Colistin groups ($p<0.05$) (Table 5).

IV. DISCUSSION

Our study recorded that the rate of *K. pneumoniae* infections in males of the block of Intensive Care units was the majority at 75%. This result was higher than the study by T.P. Vinh (2022) at the Can Tho Central General Hospital[4]. Especially, the distribution rate in the Internal Intensive Care unit was three times higher than in the Surgical Intensive Care unit (175 strains vs. 60 strains). *K. pneumoniae* related to sepsis ranked second (25.1%) after respiratory infections (66.0%). This result was consistent with the findings of N.T.T. Thuyet (2020) at the 108 Central Military Hospital (respiratory: 50%, blood: 18%) and T.P. Vinh (2022) (sputum: 63.4%).

Detailed analysis showed that the rate of *K. pneumoniae* secreting CARB in A12.1 was 75.3% (128/170), higher than that in A12.2 at 53.7% (29/54), and this difference was statistically significant ($p<0.05$). Compared to other studies, the current study results were consistent with N.T.T. Thuyet (2020) (60.4%) and Bhaskar B.H[6] (66%) - research of a level 3 hospital in India, but higher than the results of T.P. Vinh (2022) (13.8%) and X Qin (2020) in ICUs in China (54%).

The rate of ESBL-producing *K. pneumoniae* in A12.1 was 45.3%, higher than in A12.2 (37%), but this result was lower than T.P. Vinh (2022) (76.7%) and Bhaskar B.H (84%). Especially, in this study, we recorded 79 *K. pneumoniae* strains producing both CARB and ESBL, accounting for 40% in A12.1 and 20.4% in A12.2, and this difference was statistically significant ($p<0.05$). The rate of strains producing CARB, ESBL, or both varied between the Internal and Surgical Intensive Care units and differed from domestic and foreign studies. The reason may be due to differences in sample selection criteria in the study as well as the situation of anti-infection and control of the use of Betalactam and Carbapenem antibiotics in each unit.

Analyzing the drug resistance genes in 21 *K. pneumoniae* strains showed that NDM was the most common gene, accounting for 80.9%; followed by OXA 48 (76.2%), KPC (14.3%), and IMP (4.7%). This result was consistent with the order of

gene prevalence, but higher in percentage than the findings of Roberts L.W (2022) in the ICU at the National Hospital for Tropical Diseases (NDM: 54.4%, OXA 48: 46.5%, KPC: 45%). Most strains analyzed carried two genes simultaneously (NDM and OXA 48) - 66.7% and one strain carried all three resistance genes (NDM, OXA 48 and KPC). This indicates that the *K. pneumoniae* strains causing infections were a significant challenge because most of them carry antibiotic resistance genes, particularly the NDM gene, which allows bacteria to resist a wide range of antibiotics Betalactam and Carbapenem groups were available.

Regarding antibiotic resistance properties, *K. pneumoniae* was typically completely resistant to Ampicillin, with resistance rates to other tested antibiotics (Betalactam and Betalactam combination groups, Carbapenem, Quinolone) being very high, over 60%. This data was lower than the study results of N.Q. Huy[8] (2023) at the ICU of Nguyen Tri Phuong Hospital. Antibiotics with lower resistance rates included Amikacin (56% in A12.1 and 24.1% in A12.2) and Colistin (44.7% in A12.1 and 9.3% in A12.2).

Alarmingly, the antibiotic Ceftazidime-Avibactam had also become nearly ineffective against the rapidly resistant *K. pneumoniae* strains, with resistance rates up to 77.8% in A12.1 and 61.5% in A12.2. The isolated *K. pneumoniae* strains showed increasingly high antibiotic resistance rates, with the rates in the Internal Intensive Care unit always higher than in the Surgical Intensive Care unit for all tested antibiotics, with statistically significant differences for Aminoglycosides and Colistin. These results highlight the necessity for better antibiotic monitoring and antibiotic use strategies in the Intensive Care Units to minimize the emergence and spread of multidrug-resistant *K. pneumoniae* strains.

V. CONCLUSION

The appearance of *K. pneumoniae* strains producing CARB, ESBL, or both simultaneously was increasing. The most common drug-resistance gene in Intensive Care Units was NDM. The antibiotic resistance of *K. pneumoniae* to all tested antibiotics was rising, including those with strong efficacy. This posed new challenges and required special attention in managing and treating *K. pneumoniae* infections in Intensive Care environments.

REFERENCES

1. National Infection & Death Estimates for Antimicrobial Resistance (2022).

2. Gao L, Lv Y, Li Y. Analysis of the Drug Resistance of Carbapenem-Resistant *Klebsiella pneumoniae* in the China Antimicrobial Resistance Surveillance Trial

Program, 2007-2018. *Microbial drug resistance (Larchmont, NY)*. Aug 2020;26(8):944-950. doi:10.1089/mdr.2019.0299

3. Qin X, Wu S, Hao M, et al. The Colonization of Carbapenem-Resistant *Klebsiella pneumoniae*: Epidemiology, Resistance Mechanisms, and Risk Factors in Patients Admitted to Intensive Care Units in China. *The Journal of Infectious Diseases*. Mar 16 2020;221(Suppl 2):S206-s214. doi:10.1093/indices/jiz622

4. Tran, P.V., X.C. Duong, and N.H.J.T.c.Y.h.V.N. Lam. (2022). Study on the multidrug resistance situation of *Klebsiella pneumoniae* producing ESBL, carbapenemase in isolated clinical specimens at Can Tho Central General Hospital. Vietnam Medical Journal, 516(1).

5. Thuyet B.T., Nhung N. T. H., Huong N. L., Sy B. T., & Minh L. V. N. (2021). Colistin resistance rate of multidrug-resistant and carbapenem-resistant *Klebsiella pneumoniae* isolated at 108 Central Military Hospital from January 2020 to September 2020. Journal of 108 - Clinical Medicine and Pharmacy, 16(DB11).

https://doi.org/10.52389/ydls.v0i0.864.

6. Bhaskar BH, Mulki SS, Joshi S, Adhikary R, Venkatesh BM. Molecular Characterization of Extended Spectrum β-lactamase and Carbapenemase Producing *Klebsiella pneumoniae* from a Tertiary Care Hospital. *Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine*. Feb 2019;23(2):61-66. doi:10.5005/jp-journals-10071-23118

7. Roberts LW, Hoi LT, Khokhar FA, et al. Genomic characterization of multidrug-resistant *Escherichia coli, Klebsiella pneumoniae*, and *Acinetobacter baumannii* in two intensive care units in Hanoi, Viet Nam: a prospective observational cohort study. *The Lancet Microbe*. Nov 2022;3(11):e857-e866. doi:10.1016/s2666-5247(22)00181-1

8. Nguyen Q.H., Le T. T. N., Vo T. H., & Nguyen M. H. (2023) Antibiotic resistance situation of *Klebsiella pneumoniae* at Nguyen Tri Phuong Hospital from 2019 to 2022. Vietnam Medical Journal, 527(2). https://doi.org/10.51298/vmj.v527i2.5871.