European Review for Medical and Pharmacological Sciences 2023; 27: 4292-4298

The rate of transmission possibility of *KPC* and *NDM-1* producing *Klebsiella pneumoniae* in ICU: the need for strengthened infection control measures

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Abstract. – OBJECTIVE: This study aims to characterize the rate of two specific resistance genes (*KPC* and *NDM-1*) and determine the route of transmission between the sites to implement infection control measures effectively.

PATIENTS AND METHODS: This study was carried out at Viet Duc hospital in Vietnam. Bacterial isolates (*Klebsiella pneumoniae*) were collected between January 2018 and June 2019. Bacterial strains and antimicrobial susceptibility testing were performed in the VITEK 2 system.

RESULTS: A total of 100 samples from 25 patients were taken. From each patient, we collected 4 samples from 4 sites. 25 isolated strains resisted 100% to amoxicillin/acid clavulanic, piperacillin/tazobactam, and antibiotics in the cephalosporine group. Particularly in the carbapenem group, they resisted 100% to ertapenem, 96% to imipenem, and eropenem (rest was intermediate level). They have 76% sensitivity to aminoglycosides, 76% to amikacin, 60% to gentamycin, and 60% to tigecycline. *Klebsiella pneumoniae* carbapenemase (*KPC*) (+) was 24% and *NDM-1* (+) was 28%. There was no case in all four sites. Positive-*KPC* strains were mainly in two sites (4/6 = 66.67%) and positive-*NDM-1* strains were mainly in three sites (4/7 = 57.14%). Negative to both *KPC* and *NDM-1* strains were in one site (4/12 = 33.3%) and two sites (6/12 = 50%).

CONCLUSIONS: The rate of *KPC* and *NDM-1* was 24% and 28%. In accordance with high antibiotic resistance rates to common antibiotics used in Vietnam, the high rate of transmission possibility between the sites contributed to strengthen the implementation of infection control measures in the ICU setting.

Key Words:
Transmission possibility, *KPC* and *NDM-1* producing *Klebsiella pneumonia*, ICU, Infection control measures.

Introduction

Emerging multidrug-resistant gram-negative bacteria pose a danger to modern medicine because they raise morbidity, death, and health care costs. The spread of genes encoding carbapenem resistance in *Klebsiella pneumoniae* is of particular concern, with the increasing prevalence reported in Europe[1] and the USA[2]. *K. pneumoniae* carrying both iuc and *AMR* genes were found at a higher frequency than previously reported[3]. In South and Southeast Asia, *K. pneumoniae* bloodstream infections are caused by distinct sequence type than in other regions, with a higher prevalence of acquired virulence determinants.

The global epidemiology of carbapenem-resistant *K. pneumoniae* (CR-KP) is characterized by the spatially variable distribution of strains containing mostly *KPC-*, *NDM-*, and *OXA-48*-carbapenemases[4]. In Northern Vietnam, 27 clinical isolates of carbapenem-resistant *Klebsiella pneumoniae* with *KPC-2, NDM-4*, and *OXA-48* producers were collected from inpatients at Cho Ray Hospital. In this study, there was no finding about *NDM-1*[5].

Another study[6] isolated 100 strains of carbapenem-resistant *E. coli* and *K. pneumoniae* (CR-E/K) from clinical isolates in two general hospitals in Southern Vietnam. 47 (47%) of these isolates included carbapenemase-encoding genes, with 36 *NDM, 10 KPC*, and one isolate harboring both genes[6]. In the pediatric Intensive Care Unit (ICU), researching resistant strains and establishing a pan-resistant clone highlighted the importance of implementing infection control measures and optimal antibiotic dosing[7].

Moreover, investigations[7] in the Intensive Care Units in 16 Vietnamese hospitals revealed a prevalence of hospital-acquired infections of 29.5%, most commonly caused by *Acinetobacter baumannii*

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(89.2%), *Pseudomonas aeruginosa* (55.7%), and *K. pneumoniae* (14.9 %). No research has been conducted in Northern Vietnam ICUs to establish the prevalence of *KPC* and *NDM-1* and the likelihood of their transmission. This study aims to evaluate the frequency of two specific resistance genes (*KPC* and *NDM-1*) and to identify the transmission route between locations. Consequently, we may conduct efficient infection control methods.

Patients and Methods

This study was carried out at Viet Duc Hospital in Vietnam. Bacterial isolates were collected between January 2018 and June 2019. Bacterial strains and antimicrobial susceptibility testing were performed in the laboratory of the Department of Microbiology.

A total of 100 samples from 25 patients were taken. From each patient, we collected four samples from 4 sites. The four sites included bronchial fluid (sample 1), skin face (sample 2), mechanical ventilator (sample 3), and bedrail (sample 4). After confirmed bronchial fluid (sample 1) with carbapenem resistance *K. Pneumoniae*, all clinical isolates of *K. pneumoniae* obtained from the diagnostic routine at the hospital were tested for resistance to the carbapenem group (imipenem and meropenem) with antimicrobial susceptibility testing (AST) by using the VITEK 2 system (BioMérieux, Marcy-l'Étoile, France) following the CLSI guidelines in 20108. All samples were tested with KPC and NMD-1 gene using a Real-time PCR system (Model 7500, ABI). Master Mix: 2x qPCRBIO Probe Mix (PCR BioSystem, London, UK) was used. The primer and probe are detailed in Table I.

Statistical Analysis

We used the SPSS 21.0 (Statistical Package for Social Sciences version 21.0, IBM Corp., Armonk, NY, USA) software to analyze data. The measurement data, such as normal distribution, were described by the mean ± standard deviation. If the distribution was skewed in accordance with the median, then the median was used. p-value < 0.05 was considered statistically significant. All charts were built with SPSS 21.0 graphics.

Results

Patient Demographics

There were 25 patients in this study. Four samples were taken from each patient. There were a total of 100 samples. Almost 88% of the patients were male, and 12% were female. The mean age was 49.8 years old. Table II shows the patient distribution by diagnosis (n = 25).

Antimicrobial susceptibility pattern of isolates of carbapenem-resistant *K. pneumoniae* isolated at Viet Duc Hospital, Hanoi, Vietnam (all were taken from sample 1) is shown in Table III. Twenty-five isolated strains resisted 100% to amoxicillin/acid clavulanic, piperacillin/Tazobactam, and antibiotics in the cephalosporine group. Particularly in the carbapenem group, they resisted 100% to ertapenem, 96% to imipenem, and eropenem (the rest was intermediate level). They have 76% sensitivity to aminoglycosides, 76% to amikacin, 60% to gentamycin, and 60% to tigecycline.

Gene distribution of isolated patients and gene distribution by the number of sites was shown in detail in Table IV, and Table V. *KPC* (+) was 24%, and *NDM-1* (+) was 28%. There was no case in all four sites. Positive- *KPC* strains were mainly in two sites (4/6 = 66.67%), and positive-*NDM-1* strains were mainly in three sites (4/7 = 57.14%). Negative to both *KPC* and *NDM-1* strains were in one site (4/12 = 33.3%) and two sites (6/12 = 50%).

Table I. Primer.

Name	Sequence
KPC-F Primer	5'- GGC CGC CGT GCA ATA C -3'
KPC-R Primer	5'- GCC GCC CAA CTC CTT CA -3'
KPC-Probe (FAM)	5'- /56-FAM/TGA TAA CGC CGC CAA TTT GT/3BHQ_1/ -3'
NDM-F Primer	5'- GAC CGC CCA GAT CCT CAA -3'
NDM-R Primer	5'- CGC GAC CGG CAG GTT -3'
NDM-Probe (HEX)	5'-/5HEX/TGG ATC AAG CAG GAG AT/3BHQ_1/ -3'
16S rRNA-F	5'- TGG AGC ATG TGG TTT AAT TCG A -3'
16S rRNA-R	5'- TGC GGG ACT TAA CCC AAC A -3'
16SrRNA-Probe (CY5)	5'- /5Cy5/CAC GAG CTG ACG ACA GCC ATG CA/3BHQ_2/ -3'

Discussion

The most frequently occurring species of *Enterobacteriaceae*, which are found to be carbapenem-resistant and produce carbapenemases, are *Klebsiella pneumoniae* and *Escherichia coli*[2]. Carbapenem-resistant *Enterobacteriaceae* (CRE) displays various resistance profiles, depending on the type of genetic elements they harbor and the carbapenemases they produce[9]. *Klebsiella pneumoniae* carbapenemases (KPCs) of the oxacillinase-48 (*OXA-48*) type have spread globally[10]. New Delhi Metallo-β-lactamase (NDM) carbapenemases were initially identified in Sweden in 2008 and have spread worldwide rapidly.

Because carbapenemase-producing *Klebsiella pneumoniae* are often resistant to most β-lactam antibiotics and many other non-β-lactam molecules, the therapeutic options available to treat the infection with these strains are limited to colistin, polymyxin B, fosfomycin, tigecycline, and selected aminoglycosides[4]. In our study, the sensitivity was noted with an aminoglycoside, amikacin, gentamycin, and tigecycline. The optimal treatment of carbapenemase-producing *Klebsiella pneumonia* infection is not clearly defined. Some newer agents promise to treat infections due to *KPC* producers; however, effective options for treating *NDM* producers remain elusive[8].

Table II. Patient distribution by diagnosis (n = 25).

Diagnosis	Number of patients (n = 25)
Multi-trauma	12 (48%)
Brain trauma	9 (36%)
Hemorrhage stroke	1 (4%)
Femur neck fracture	1 (4%)
Septic shock	1 (4%)
Post-operation abscess	1 (4%)

Table III. Antimicrobial susceptibility pattern.

Antibiotics	Level (%) Sensitivity	Intermediate	Resistance
Amoxicillin/a. clavulanic	0	0	100
Ticarcillin/a. clavulanic	0	0	100
Piperacillin/tazobactam	0	0	100
Cefuroxime	0	0	100
Cefotaxime	0	0	100
Ceftriaxone	0	0	100
Ertapenem	0	0	100
Ciprofloxacin	8	0	92
Gentamicin	60	0	40
Amikacin	76	4	20
Imipenem	0	4	96
Meropenem	0	4	96
Co-trimoxazole STX	8	0	92
Tigecycline	60	40	0

Table IV. Gene distribution of isolated patients.

Gene	ESBL (+)	(-)	*KPC* (+)	*NDM-1* (+)	*KPC and NDM-1* (-)
Number (Percentage)	19 (76%)	6 (24%)	6 (24%)	7 (28%)	12 (48%)

Table V. Gene distribution by number of sites.

	Total	One site	Two sites	Three sites	Four sites
Negative to both KPC and NDM-1	(12)	4	6	2	0
Positive-KPC	(6)	1	4	1	0
Positive-NDM-1	(7)	1	2	4	0

Molecular Perspectives

ST258

Molecular and genetic studies[4] analyzed the mechanisms by major *K. pneumoniae* clones, such as *ST258* and *ST11*, which have become globally prevalent. The *ST258* clonal group dominates Europe and the USA, whereas *ST11* is more common in East Asian countries. *ST15* (*KPC-2*) is another *K. pneumoniae* clonal group associated with the production of extended-spectrumsβ-lactamases (*ESBLs*) and carbapenemases and has been indicated in clinical cases and hospital outbreaks worldwide[4]. Distinct *ST258* subpopulations have caused both device-associated and ward-associated outbreaks[11]. Molecular dissection revealed the emergence of carbapenem-resistant multilocus sequence type 258 *K. pneumoniae*[12]. One way of *ST258* molecular evolution was the horizontal transfer of the capsule olysaccharide gene region[13]. *K. pneumoniae ST258* harboring *KPC-2* was characterized by two patterns of dispersion[14]. It also involved an outbreak in a hospital in Greece[15,16], even mainly due to a hyperepidemic clone[17]. *K. pneumoniae ST258* harboring *KPC-3* involved an outbreak in a Mexican medical center[18] and in Italian Intensive Care Units[19]. Interestingly, a multimodal infection control program was implemented, and the outbreak was controlled without closing the ICU[19]. It evolved the development of effective control and treatment strategies for outbreaks due to multidrug-resistant *K. pneumonia*, such as continued surveillance, prevention, and control efforts in the healthcare setting.

NDM-1

New Delhi Metallo beta-lactamase (*NDM-1*) emerged as a cause of an outbreak in the hospital[20]. Early detection of a specific *NDM-1*-containing lineage would have alerted the high-dependency ward staff to intervene[21]. It is critical that *NDM-1*-producing *Klebsiella pneumoniae* caused an in-hospital outbreak in many countries, such as Turkey[22] and Lebanon[23]. *NDM-1* also appeared in other organisms, such as *A. baumannii*, producing *NDM-1*[24]. The dual mechanism of action may help deal with infections caused by *NDM-1*-producing pathogens[25].

Reservoir

Numerous reports have warned about the likely spread into the community from healthcare settings because of the highly transmissible nature of plasmid-borne carbapenemases. The presence of CRE in the community poses an urgent public health threat, identifying percentages ranging from 0.04% to 29.5% of either community-associated or community-onset CRE among their samples, with US-based studies[26] alone ranging from 5.6 to 10.8%. The hospital environment is a potential reservoir of bacteria with plasmids conferring carbapenem resistance. In the hospital, a study[27] revealed a diverse reservoir of bacterial plasmids conferring carbapenem resistance and highlighted a potential environmental reservoir of mobile elements that may contribute to the spread of resistance genes. Among patients admitted to Vietnamese hospitals, the prevalence of colonization with carbapenem-resistant Enterobacteriaceae (CRE) was high (52%). There spread of CRE in transmission to hospitalized patients was rapid, with an average of 4.2% per day of CRE colonisations. Especially in the Neonatal ICU, CRE colonization increased from 32% at admission to 87% at discharge, significantly associated with mortality[28].

Transmission Route

The epidemic of carbapenem-resistant *Klebsiella pneumoniae* in Europe is driven by nosocomial spread[29]. Patients can acquire CRE through multiple pathways: endogenously through antibiotic selective pressure on intestinal microbiota, exogenously through horizontal transmission, or through a combination of these factors[30]. Horizontal plasmid transfer spreads the resistance mechanism to new bacteria[27]. Horizontal gene transfer (HGT) is a significant factor in the rapid spread of resistance. Multiple HGT methods release genes from their typical vertical inheritance. The transfer of genetic material between strains and species is made possible through plasmid conjugation, bacteriophage transduction, and extracellular DNA transformation. It allowed an antibiotic resistance gene (ARG) to transfer resistance to numerous unrelated bacteria, serving as an outbreak agent. HGT must be incorporated into hospitals and along with other clinical antimicrobial resistance prevention programmes[31]. *K. pneumoniae* spreading in hospital environments correlates with the degree of resistance, and carbapenemase-positive isolates have the highest transmissibility[32].

Outbreak

The high rate of transmission combined with multiple transmission routes leads to an outbreak in the hospital. Using whole-genome sequencing (WGS) to demonstrate multiple genetic modes of transmission is a successfully controlled outbreak. WGS of outbreak KPC isolates demonstrated

bla$_{KPC}$ dissemination *via* horizontal transposition (*Tn4401a*), plasmid spread (*pKpQIL-D2*), and clonal spread (*K. pneumonia ST661*). Dissemination of *bla*$_{KPC}$ emphasized its high transmission potential and the need for enhanced control efforts[33]. The outbreak happened due to the various types, including *NDM-1*-producing *Klebsiella pneumoniae ST76* and *ST37* (isolates in neonates)[34], *KPC-3*-producing *Klebsiella pneumoniae* (*ST512*) (in Spain)[35], *KPC-3*-encoding plasmid (in Italy)[36]. Health-care-associated infections were independent risk factors for CRE colonization[28]. Patients with CRKPs were put under strict contact isolation, along with appropriate infection control measures. Contact isolation, hand hygiene, environmental cleaning, and staff education may control the CRKP outbreak in the acute care setting[37]. Hand hygiene is critical when person-to-person transmission was found with the type of *OXA-48*-producing *Klebsiella pneumoniae*[38]. Environmental cleaning is essential because it reduces healthcare-associated infections[39] and eliminates a reservoir of bacteria in particular with plasmids conferring carbapenem resistance[27].

Conclusions

The rate of *KPC* and *NDM-1* was 24% and 28%. In accordance with high antibiotic resistance rates to common antibiotics used in Vietnam, the high transmission possibility rate between the sites contributed to strengthened implementation of infection control measures in the ICU setting.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

The Viet Duc Hospital Ethics Committee approved the study and authorized its conduct and follow-up (No. 1614 of 20 November 2017). The study was in line with the Declaration of Helsinki.

Informed Consent

Individual patient consent for inclusion in the study was obtained. Written informed consent was provided from all participants or legal's representatives.

Acknowledgments

Not applicable.

Authors' Contributions

All authors made substantial contributions to conceptualization and design, data acquisition, data analysis, and interpretation, took part in the drafting of the initial manuscript and revising it critically, gave final approval of the version to be published, agreed to submit to the current journal, and agreed to be accountable for all aspects of the work.

Funding

The authors received no specific funding for this work.

Conflict of Interest

The authors declare that they have no conflicts of interest in this work.

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