Hypervirulent *Klebsiella pneumoniae* as a hospital-acquired pathogen in the intensive care unit in Mansoura, Egypt

Rasha EL-Mahdy^{1,*}, Ghada El-Kannishy², Hassan Salama³

Abstract

Introduction Hypervirulent *Klebsiella pneumoniae* (hvKP) are variants of *K. pneumoniae* that come up worldwide. hvKP is known in community-acquired infections but little is known about its role in hospital-acquired (HA) infections. The aim of this study was to evaluate the frequency of hvKP among HA *K. pneumoniae* infections in the intensive care unit (ICU) and to compare virulence and antibiotic susceptibility between hvKP and classical *K. pneumoniae* (cKP).

Methods String test, biofilm formation, serum bactericidal assay, capsular polysaccharide genes (*K1*, *K2*, *K5*, *K20*, *K54*, *K57*), virulence genes: *rmpA*, *rmpA2*, *iucA*, *iroB* and antimicrobial susceptibility were assessed in HA *K. pneumoniae* strains isolated from the ICU in Mansoura, Egypt.

Results Probable hvKP represented 4 out of 65 (6.2%) *K. pneumoniae*. *K1* and *K2* genes were present in 2 and 1 isolate respectively in probable hvKP. *rmpA* genes were significantly associated with hvKP; at the same time biofilm production and serum resistance were not significantly associated with the hypervirulent group. There was no significant difference between hvKP and cKP strains in terms of resistance pattern.

Conclusion hvKP in critically ill patients from the ICU may form a new threat especially in the presence of antibiotic resistance. Although the validity of the string test in detecting metastatic *Klebsiella* is questionable, it is a simple and easy test that can be done in any laboratory indicating the presence of this organism. Serotypes and genomic background may provide helpful and confirmatory tools to diagnose hvKP.

Keywords hospital-acquired, hypervirulent, intensive care unit, *Klebsiella pneumoniae*.

Introduction

Klebsiella pneumoniae can cause both community- and hospital-acquired (HA) infections.¹ There are two different groups of *Klebsiella pneumoniae*: classical (cKP) and

hypervirulent (hvKP).² cKP used to describe the commonly known strains of *K. pneumoniae*, which are responsible for most HA infections, in immunocompromised patients.³ The hvKP was first identified in Taiwan in 1986;⁴ these new variants have the ability of causing metastatic and life-threatening infections in healthy persons in the community.⁵ Recently, hvKP infection is increasingly reported in other countries.^{6,7}

Several virulence factors have been detected in *K. pneumoniae*, such as the capsule that protects bacteria from both phagocytosis and lethal serum factors, plasmid-borne *rmpA* (regulator of mucoid phenotype A), fimbriae, lipopolysaccharides and siderophores.^{3,6,8} The kind and number of virulence factors influence the type of *K. pneumoniae* infections.⁹ Moreover, the infectivity is exacerbated by the capacity of *K. pneumoniae* to acquire multiple drug resistance.¹

Many studies have reported the role of hvKP in community-acquired infection,^{4,5} but there are limited studies on its role in HA infections.

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This study was conducted to evaluate the frequency of hvKP among HA *K. pneumoniae* infections in the intensive care unit (ICU) and to compare virulence and antibiotic susceptibility between hvKP and cKP.

Methods

A cross-sectional study was conducted for a period of six months from June to December 2015 in 3 ICUs (2 medical ICUs and 1 surgical ICU) in Mansoura University Hospital, Mansoura, Egypt. The study was approved by the Institutional Research Board at the Faculty of Medicine, Mansoura University (No. R/16.12.75). Infections were considered as HA when a new infection developed 48 hours after patient admission. Samples were collected from patients with HA infections. Non-repetitive consecutive isolates were identified as *K. pneumoniae* by Gram stain, colony morphology, Kligler iron agar, oxidase test, Lysine iron agar, methyl red, Voges-Proskauer test, citrate tests, motility indole ornithine,¹⁰ and confirmed by API 20E (BioMérieux, Marcy l'Étoile, France).

Antibiotic susceptibility testing

Antibiotic susceptibility testing was done for all isolates of *K. pneumoniae* by the disk diffusion method according to CLSI guidelines.¹¹ The following antimicrobial agents were tested: ampicillin, amoxicillin-clavulanate, cefoperazone-sulbactam, cefoxitin, aztreonam, cefepime, ceftazidime, cefotaxime, ciprofloxacin, gentamicin, imipenem, meropenem (Oxoid, Altrincham, Cheshire, UK).

Extended-spectrum beta lactamase production (ESBL) and plasmid-mediated AmpC β -lactamases (pAmpC) were tested by double disk synergy test and modified three dimensional test respectively.^{12,13}

String test

Bacterial colonies on an agar plate were extended by a standard bacteriological loop. If a mucoviscous string >5 mm in length was formed, it was considered positive string and the strain was identified as hypermucoviscous.¹⁴

Serum resistance assay

The serum resistance assay was done as previously described.¹⁵ Then, survival of bacteria in normal human serum was documented over a period of three hours and classified into six grades. The strains were considered as highly sensitive (grades 1 and 2), intermediately sensitive (grades 3 and 4), or resistant (grades 5 and 6).¹⁶

Biofilm formation

Biofilm formation was evaluated by the semi-quantitative assay in 96-well flat bottom plates, as previously described.¹⁷

Capsular polysaccharide genotyping, virulence factors and β -lactamase genes detection

Genomic DNA was extracted by Gene JET genomic DNA purification kit (Thermo Fisher Scientific, Waltham, MA, USA). Detection of capsular serotype-specific genes *K1*, *K2*, *K5*, *K20*, *K54*, *K57*, virulence genes: *ompA*, *ompA2*, *iucA*, and *iroB* and β -lactamase genes: *SHV* and *TEM* was performed by polymerase chain reaction. The presence of *iucA*, or *iroB* genes was used to identify probable hvKP. Primers used in this study are listed in Table 1.

PCR conditions used for capsular genotyping were applied as previously described.⁵ Multiplex PCR was done for *ompA*, *ompA2* in the same conditions as previously described.⁶ PCR conditions for *iucA* included an initial denaturation at 95°C for 15 min, followed by denaturation at 95°C for 15 s, annealing at 49°C for 15 s, and extension at 72°C for 1 min for 30 cycles, followed by a final extension for 10 min at 72°C. PCR conditions for *iroB* were the same as those used in *iucA* but the annealing temperature was 55°C. PCR conditions for *SHV* and *TEM* β -lactamase were applied as previously described.¹⁸

Statistical analysis

Data were statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16 (SPSS Inc, Chicago, IL, USA). Qualitative data are described as numbers and

percentages. The Chi-square test or Fisher's exact test were used for comparison between groups, as appropriate. Results with $p < 0.05$ were considered significant.

Table 1. Specific primers used for capsule genotyping and for various virulence genes of *K. pneumoniae*

Gene	Primers sequence	References
K1	5'-GTAGGTATTGCAAGCCATGC-3' 5'-GCCCAGGTTAATGAATCCGT-3'	5
K2	5'-GGAGCCATTGAAATTCGGTG-3' 5'-TCCCTAGCACTGGCTTAAGT-3'	5
K5	5'-GCCACCTCTAAGCATATAGC-3' 5'-CGCACCAGTAATTCCAACAG-3'	5
K20	5'-CCGATTCCGGTCAACTAGCTT-3' 5'-GCACCTCTATGAACTTTCAG-3'	5
K54	5'-CATTAGCTCAGTGGTTGGCT-3' 5'-GCTTGACAAACACCATAGCAG-3'	5
K57	5'-CGACAAATCTCTCCTGACGA-3' 5'-CGCGACAAACATAACACTCG-3'	5
<i>mpA</i>	5'-ACTGGGCTACCTCTGCTTCA-3' 5'-CTTGCATGAGCCATCTTTCA-3'	6
<i>mpA2</i>	5'-CTTTATGTGCAATAAG-GATGTT-3' 5'-CCTCCTGGAGAGTAAGCATT-3'	27
<i>iucA</i>	5'-ATAAGGCAGGCAATCCAG-3' 5'-TAACGGCGATAAACCTCG-3'	31
<i>iroB</i>	5'-TGTGTGCTGTGGGTGAAAGC-3' 5'-ATGTTCCGGTGAGATTCGCCAGT-3'	31
<i>SHV</i>	5'-TCAGCGAAAAACACCTTG-3' 5'-CCCGCAGATAAATCACCA	18
<i>TEM</i>	5'-GAGTATTCAACATTTCCGTGTC-3' 5'-TAATCAGTGAGGCACCTATCTC-3'	18

Results

Patient characteristics

A total number of 65 isolates of *K. pneumoniae* were isolated from 65 patients with hospital-acquired infections in the ICUs of Mansoura University Hospital. The strains were isolated as follows: 11 from blood, 21 from urine, 26 from respiratory secretions and 7 from wound.

Four strains were identified as probable hvKP based on being positive for either *iucA*, or *iroB* gene. All hvKP strains were MDR. All hvKP were isolated from Egyptian patients, none of these patients had travelled abroad in the last year. No metastatic infection was reported in hvKP-infected patients. Characteristics of these hypervirulent strains are shown in Table 2.

A significantly higher number of hvKP was recovered from diabetic patients ($p=0.004$). Otherwise, no significant differences in the underlying conditions of patients were recorded between hvKP and cKP strains. Differences between the clinical characteristics of patients with hvKP and cKP are shown in Table 3.

Comparison between hvKP and cKP isolates

In the hypervirulent strains, the capsule K1 and K2 genes were present in two and one of the isolates respectively; no K5, K20, K54 and K57 serotype genes were found. Two isolates were positive for both *mpA* and *mpA2* genes (50%), one isolate (25%) was positive for *mpA2* only. Hypermucoviscosity was detected in all hvKP isolates and 8.2% of cKP. At the same time, all cKP isolates were non-typable and they did not carry any of the tested virulence genes. There was no significant difference between hvKP and cKP strains in terms of serum resistance or biofilm formation Table 4.

Antimicrobial susceptibility testing

There was no significant difference between hvKP and cKP strains in the resistance pattern. The results of antimicrobial susceptibility testing for hvKP and cKP are summarized in Table 5.

Discussion

Hypervirulent *Klebsiella pneumoniae* are rising variants that cause serious community-acquired infection.³ In the current study, probable hvKP identified by the presence of the *iucA* or *iroB* gene represented 6.2% of HA *K. pneumoniae* infections in ICUs. On the other hand, a higher prevalence of the hvKP in different HA infections has been previously reported.^{2,19}

The hypermucoviscosity phenotype was detected in 13.8% of all *K. pneumoniae* isolates. These phenotypes were more significantly detected in hvKP. In previous studies, the prevalence of hvKP varied from 7.8% to 25.4,^{20,21} whereas another study conducted in Egypt reported that about 40% of *K. pneumoniae* isolates were hypermucoviscous.²²

Table 2. Microbiological and genetic characteristics of hypervirulent *Klebsiella pneumoniae* strains

No	Sample	Biofilm	Serum resistance	Capsule	<i>ompA</i> <i>ompA2</i>	String test	<i>iucA</i>	<i>iroB</i>	SHV	TEM
1	Endotracheal aspirate	+	Grade 6	K1	<i>ompA</i> , <i>ompA2</i>	+	+	-	+	-
2	Wound	+	Grade 5	K1	<i>ompA</i> <i>ompA2</i>	+	+	+	-	-
3	Endotracheal aspirate	-	Grade 6	-	-	+	+	-	-	-
4	Wound	+	Grade 5	K2	<i>ompA2</i>	+	+	-	-	-

Grade 5 – the viable count after 1, 2, and 3 hours was >100%; however, the viable count fell sometime in the 3-hour period. **Grade 6** – the viable count after 1, 2, and 3 hours was >100% of the inoculum and increased during the 3-hour period.

Table 3. Clinical characteristics of patients with hypervirulent *Klebsiella pneumoniae* (hvKP) and classical *Klebsiella pneumoniae* (cKP)

Variable	hvKP (n=4)	cKP (n=61)	P-value	Odds ratio	95% confidence interval
Age >60 years	2	30	1	1.033	0.137-7.815
Male	1	40	0.138	5.714	0.559-58.379
Prolonged hospitalization	1	45	0.072	8.438	0.818-87.065
Coexisting condition					
Diabetes mellitus	4	13	0.004*	1.308	1.005-1.702
Liver cirrhosis	2	12	0.200	4.083	0.521-32.010
Chronic renal failure	1	2	0.176	9.833	0.684-141.432
Neurological disease	3	16	0.072	8.438	0.818-87.065
Pulmonary disease	2	11	0.176	4.545	0.576-35.871
Malignancy	1	2	0.176	9.833	0.684-141.432
Invasive devices					
Endotracheal intubation	3	29	0.355	3.310	0.326-33.627
Urinary catheter	3	30	0.613	3.100	0.305-31.487
Central venous catheter	2	13	0.226	3.692	0.474-28.783
Infection					
Bloodstream infections	0	11	1	0.926	0.859-0.998
Urinary tract infections	0	21	0.296	0.909	0.828-0.998
Pneumonia	2	24	1	1.542	0.203-11.693
Surgical site infections	2	5	0.054	11.2	1.288-97.404
Mortality	2	6	0.070	9.167	1.086-77.402

Prolonged hospitalization was defined as >2 weeks. Data are no. of patients.

*A p-value of <0.05 was considered to be statistically significant.

The capsule is a major virulence factor in *K. pneumoniae*, with 78 capsular polysaccharides identified. K1, K2, K5, K16, K20, K54, K57 and KN1, are documented in hvKP.^{3,5} In this study, while all cKP isolates were non-typable, serotypes

K1, K2 have been recognized in 2 and 1 isolate respectively of hvKP.

The *ompA* and *ompA2* are genes that regulate the synthesis of extracellular polysaccharide capsule.³ In this study, these genes were significantly associated with hvKP isolates, as

Table 4. Comparison of serotypes and virulence genes of hypervirulent *Klebsiella pneumoniae* (hvKP) and classical *Klebsiella pneumoniae* (cKP)

Variable	hvKP (n=4)	cKP (n=61)	P-value	Odds ratio	95% confidence interval
Serotypes					
K1	2	0	0.003**	0.032	0.008-0.124
K2	1	0	0.062	0.047	0.016-0.141
K5	0	0	N/A	N/A	N/A
K20	0	0	N/A	N/A	N/A
K54	0	0	N/A	N/A	N/A
K57	0	0	N/A	N/A	N/A
Non-typable	1	61	<0.001*	62	8.873-433.212
Virulence					
<i>mpaA</i> or <i>mpa2</i>	3	0	<0.001*	0.016	0.002-0.113
Hypermucoviscosity	4	5	<0.001*	1.8	1.003-3.229
Biofilm formation	3	27	0.328	3.778	0.372-38.398
Serum resistance	3	41	1	1.463	0.143-14.973

N/A – not applicable.

Data are no. of patients.

*A p-value of <0.05 was considered to be statistically significant.

Table 5. Antimicrobial resistance pattern of hypervirulent *Klebsiella pneumoniae* (hvKP) and classical *Klebsiella pneumoniae* (cKP)

Variable	hvKP (n=4)	cKP (n=61)	P-value	Odds ratio	95% confidence interval
Ampicillin	4	61	N/A	N/A	N/A
Amoxicillin-clavulanate	3	55	0.373	3.056	0.273-34.190
Cefoperazone-sulbactam	3	51	0.533	1.700	0.160-18.050
Cefoxitin	4	58	1	0.935	0.876-0.999
Cefotaxime	4	56	1	0.933	0.872-0.999
Ceftazidime	3	58	0.229	6.444	0.507-81.988
Cefepime	4	57	1	0.934	0.874-0.999
Ciprofloxacin	2	46	0.278	3.067	0.397-23.697
Gentamicin	3	55	0.373	3.056	0.273-34.190
Aztreonam	4	57	1	0.934	0.874-0.999
Imipenem	0	8	1	1.075	1.001-1.155
Meropenem	0	10	1	1.078	1.001-1.161
ESBL	1	29	0.618	0.368	0.036-1.068
pAmpC	2	34	1	0.794	0.105-6.011

Data are no. of patients.

ESBL – extended spectrum β -lactamase; N/A – not applicable.

previously reported.^{23,24} Moreover, they were only present in hvKP strains with serotypes K1, K2 and not present in any non-typable strains. These findings are in line with other published results, which state that they are extremely uncommon in serotypes other than K1, K2, K5, K16, K20, K54, K57.²⁵ On the other hand, Zhang et al.²⁶ found a lack of direct correlation between

hypermucoviscosity and the expression of *mpaA* in hvKP strains.

There was no significant difference in biofilm production and serum resistance between hvKP when compared to cKP. Yan et al.²³ reported that there was a significant association between these genes and hvKP but not with cKP. On the contrary, Fang et al.¹⁴ detected high serum

resistance in hvKP. Virulence genes were detected at a lower rate compared to other studies.²⁷ This difference may be due to geographic differences or because other studies were conducted in community-acquired infections.⁹

The coexistence of virulence factors such as the *ompA* gene, siderophores and biofilm production with hvKP strains carrying genes for K1 and K2 indicate a high virulence of these strains. It has also been previously stated that strains serotype K1 or K2 are particularly virulent.²⁸ In addition, these isolates carry also *ompA* genes. The presence of *ompA* may suggest the presence of a plasmid containing other virulence-associated genes.⁸ Recently, Zhang et al.¹⁹ defined hvKP by positive aerobactin isolates. For these reasons, using the string test for defining hvKP may not be adequately sensitive. Different virulence factors other than hypermucoviscosity participate more significantly in the virulence of *K. pneumoniae* isolates.²⁹

In agreement with a previous study, diabetes mellitus is considered a predisposing factor for acquiring hvKP infections,¹⁹ while there was no significant difference between hvKP and cKP infections with other underlying diseases.^{7,23,30}

Although hvKP isolates were considered less resistant than cKP, multidrug resistance and even carbapenem resistance emerged in hvKP isolates.²⁴ In this study, although all hvKP isolates were sensitive to carbapenem, they were MDR. Moreover, one isolate was an ESBL producer and this isolate carried the *SHV* gene; another two isolates were pAmpC producers. The rate of resistance among our hvKP isolates was higher than that from previous studies.^{5,19,23}

Conclusion

hvKP detected in the ICU may form a new threat for critically ill patients especially if they are associated with antibiotic resistance. Although the validity of the string test in detecting metastatic *Klebsiella* is questionable, it is a simple and easy test that can be done in any laboratory indicating the presence of this organism. Serotypes or aerobactin genomic background may provide helpful and confirmatory tools to diagnose hvKP.

Authors' contributions statement: RE, GE, HS designed the study. RE did microbiology, molecular biology laboratory work, the analysis and interpretation of data. All authors prepared the first draft, read and approved the final manuscript.

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