JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Emerging Problems in Infectious Diseases

Microbiological characteristics of hypermucoviscous *Klebsiella pneumoniae* isolates from different body fluids

Xiumei Xiao[1]*, Bei Yao[1]*, Qingtao Zhou[2], Jie Zhang[1]

[1] *Department of Laboratory Medicine, Peking University Third Hospital, No. 49 North Garden Road, Haidian District, Beijing 100191, China*
[2] *Department of Respiratory Medicine, Peking University Third Hospital, Beijing 100191, China*

* These authors contributed equally to this work

Abstract

Introduction: Reports of hypermucoviscous *Klebsiella pneumoniae* (hvKP) isolated from fluids other than blood or abscess are rare. The aim of the study was to compare clinical and microbiological characteristics of hvKP found in blood or abscess fluid with those isolated from other loci.

Methodology: A total of 24 non-repetitive hvKP isolates were collected from January 2013 to June 2014 from patients with hvKP infections. There were 15 in Group 1 (fluid other than blood or abscess) and 9 in Group 2 (blood or abscess fluid). Medical records of all patients were reviewed. Capsular polysaccharide (CPS) typing, virulence factor determination, and multilocus sequence typing (MLST) of hvKP isolates were performed.

Results: Seventeen sequence types (STs) and 6 capsular serotypes were identified. Type $K2^{CC65}$ was most commonly identified in Group 1 and type $K2^{CC86}$ in Group 2. Deletion of pLVPK-derived loci were found in K2 and non-K1/K2 hvKP strains. Two virulent genes, *fimH* and *ycfM*, were identified more frequently in Group 2 than in Group 1. There was no difference in the frequency of other virulent genes or serotypes in the two groups. Two imipenem resistant hvKP isolates (cr-hvKP) were found in non-blood or abscess samples.

Conclusions: hvKP isolated from different body fluids had similar clinical and microbiological characteristics. cr-hvKP identified in non-blood or abscess samples should raise our attention to the challenging situation and management of hvKP infection.

Key words: Hypermucoviscous *Klebsiella pneumoniae*; microbiological characteristics; virulence; fluid; abscess.

J Infect Dev Ctries 2017; 11(9):672-678. doi:10.3855/jidc.8132

(Received 18 January 2016 – Accepted 13 September 2016)

Introduction

Klebsiella pneumoniae infections commonly occur in hospital and long-term care facilities, in patients with serious underlying disease. A new hypermucoviscous clinical variant of *K. pneumoniae* (hvKP) found in community-acquired pyogenic liver abscesses (CA-PLA) and septic endophthalmitis was reported in Taiwan in 1986 [1]. Life-threatening liver abscesses, pneumonia, meningitis, bloodstream infections (BSI) or endophthalmitis caused by hvKP have been increasingly reported in the USA, Brazil, Germany, Japan, and Australia [2-6]. These infections are often community-acquired [7-11].

The hypermucoviscous (hv) phenotype is a distinguishing factor of hvKP strains. hvKP is considered to be more virulent than hv-negative strains and this phenotype is commonly found in *K. pneumoniae* strains which cause CA-PLA and BSI [8,12,13]. More importantly, they exhibit a higher tendency to metastatic spread. These two traits contribute to the high mortality rate associated with hvKP infection.

hvKP is more resistant to phagocytosis by polymorphonucleated neutrophils, less sensitive to killing by serum complement, and more virulent in animal studies [14-18]. Previous reports have focused on hvKP infections isolated from abscess and blood fluids. We isolated hvKP from urine and tracheal secretions, evaluated their clinical and microbiological characteristics, and compared them to those of isolates obtained from blood and abscess fluid.

Methodology

Bacterial isolates

All isolates were obtained from patients seen at Peking University Third Hospital (PUTH), a university-affiliated medical center with a 1,498-bed capacity and 79,000 hospital admissions per year. A total of 533 non-

repetitive *K. pneumoniae* clinical isolates were identified by VITEK GN card (bioMe'rieux, Marcy l'Etoile, France) from January 2013 to June 2014. All samples were stored at −80°C prior to genetic and virulence testing. An hv phenotype test was performed on all isolates to distinguish hvKP from classic *K. pneumoniae* (cKP) [12]. The presence of a viscous string greater than 5 mm in length with a bacteriology inoculation loop on bacterial cultures grown overnight on 5% sheep blood agar plate at 37°C was regarded as diagnostic of hvKP.

The first hvKP isolate from each patient was used for further investigation. hvKP isolated from asymptomatic patients was classified as colonization and was not included in this study. Infection was considered to be nosocomial if it was diagnosed ≥48 h after admission and the patient had no evidence of clinical infection at the time of admission. Symptomatic infections diagnosed within 48h of admission were considered to be community acquired [19,20]. hvKP strains not isolated from blood or abscess fluid were Group 1. hvKP strains isolated from blood or abscess fluid were Group 2.

Antimicrobial susceptibility testing

Antimicrobial susceptibility to 20 antimicrobial agents, including ampicillin, ampicillin-sulbactam, piperacillin, piperacillin-tazobactam, cefazolin, cefuroxime, ceftriaxone, ceftazidime, cefepime, aztreonam, imipenem, meropenem, cefotetan, levofloxacin, ciprofloxacin, gentamicin, tobramycin, amikacin, nitrofurantoin, and trimethoprim-sulfamethoxazole, was performed using VITEK panels (bioMérieux, Marcy l'Étoile, France). Results were interpreted according to current interpretive standards of the Clinical Laboratory Standards Institute (CLSI) [21]. *Escherichia coli* ATCC 25922 was used as a quality control strain for susceptibility testing.

Capsular polysaccharide (CPS) typing and multilocus sequence typing (MLST) of hvKP

The capsular serotypes K1, K2, K5, K20, K54, and K57 were detected by PCR as previously described [22]. Product from each PCR was visualized by 1.5% agarose gel electrophoresis and then sequenced commercially. The BLAST program at http://www.ncbi.nlm.nih.gov was used for final serotype identification. MLST was performed according the protocols for *K. pneumoniae* provided on the MLST website (http://bigsdb.web.pasteur.fr/klebsiella/klebsiella.html) . MLST allelic profiles were characterized using the MLST database. Sequence types (STs) were analyzed using eBURST version 3.0. Clonal complexes (CCs) were defined as groups of two or more isolates sharing at least 6 identical alleles.

Detection of virulence factors

The presence of 12 genes encoding the virulence factors MrkD, KfuBC, Cf29a, FimH, Uge, WabG, UreA, YcfM, EntB, YbtS, IroN, and AllS, were determined by PCR using previously described primers [23,24]. pLVPK-derived genetic loci (*terW-iutA-rmpA-silS)* and the *repA* gene were detected by PCR, using specific primers for *terW, iutA, rmpA, silS* and *repA* [25]. After 5 minutes at 94°C, there were 35 cycles of 94°C, 30 seconds; the annealing temperature, 30 seconds.; and 72°C, 1 minute followed by a final elongation of 5 minutes at 72°C.

Statistical analysis

Data were analyzed using the statistical package SPSS 17.0 for Windows. The Fisher's exact test or Chi-square test were used for categorical variables. All statistical tests were 2 tailed and a p value ≤0.05 was considered statistically significant. Descriptive data were reported as mean ± SD.

Table 1. Distribution of the sample types among cKP and hvKP defined as colonization and infection.

Sample type	hvKP- colonization	hvKP- infection	cKP	Total
Abscess fluid	0	6	3	9
Blood	0	3	41	44
Tracheal secretion	11	11	290	312
Urine	3	4	92	99
Superficial secretion	2	0	15	17
Genital tract Secretion	0	0	18	18
Bile	0	0	13	13
Abdominal drainage	0	0	21	21
Total	**16**	**24**	**493**	**533**

Ethical approval

The study was approved by the Institutional Review Board of PUTH.

Results

Bacterial isolates and clinical characteristics

Forty patients admitted to PUTH during 18 months-long period were identified as having cultures positive for hvKP (7.5%, 40/533) and 493 had cKP (Table 1). hvKP was most commonly found in abscess fluid (66.7%, 6/9), followed by superficial secretions (11.8%, 2/17), urine (7.07%, 7/99), tracheal secretions (7.05%, 22/312) and blood (6.82%, 3/44).

Twenty-four patients had infections and 16 were colonized with hvKP. Colonized fluids included tracheal secretions, urine and superficial secretions. Eleven of 22 (50%) hvKP tracheal isolates and 4 of 7 (58.1%) hvKP urine isolates were associated with infection. Group 1 patients were diagnosed with hvKP pneumonia (n = 11) and urinary tract infections (n = 4). Group 2 patients were identified with an hvKP liver abscess (n = 6) or BSI (n = 3).

Men older than 60 years were predominantly affected with community acquired infections. Patients were generally toxic on admission and frequently required invasive monitoring or care. Over 80% of patients recovered and were discharged. The clinical characteristics of each hvKP group were similar (Table 2).

Antimicrobial susceptibility

The antimicrobial resistant rates of the 24 hvKP isolates were ampicillin 100%, ampicillin-sulbactam 20.8%, piperacillin 29.2%, piperacillin-tazobactam

Table 2. Comparison of clinical characteristics.

Characteristics	Groups, n (%)		
	Group 1* (n = 15)	Group 2** (n = 9)	*p* Value
Age,＞60 years	12 (80.0)	4 (44.4)	0.099
Sex			
Male	11 (73.3)	6 (66.7)	1.000
Female	4 (26.7)	3 (33.3)	
Community-acquired	9 (60.0)	8 (88.9)	0.191
Hospital-acquired	6 (40.0)	1 (11.1)	0.156
Underlying diseases			
Biliary tract diseases	1 (6.7)	1 (11.1)	1.000
CABG	1 (6.7)	1 (11.1)	1.000
Spine surgery	2 (13.3)	0	0.511
History of intra-abdominal surgery	3 (20.)	0	0.266
Hepatitis B virus	1 (6.7)	0	1.000
Hyperlipidemia	4 (26.)	0	0.259
Respiratory tract disorders	2 (13.3)	1 (11.1)	1.000
Cardiovascular diseases	7 (46.7)	1 (11.1)	0.178
Diabetes	5 (33.3)	4 (44.4)	0.678
Tuberculosis	2 (13.3)	0	0.511
Non-hepatic malignancies	3 (20.0)	2 (22.2)	1.000
Immunosuppressive therapy	3 (20.0)	0	0.266
Alzheimer's disease	1 (6.7)	0	1.000
Cerebrovascular accident	5 (33.3)	0	0.118
Metastatic infection	0	1 (11.1)	0.375
Use of invasive devices			
Nasogastric feeding tube	12 (80.0)	6 (66.7)	0.635
Total parenteral nutrition	7 (46.7)	3 (33.3)	0.678
Bladder catheter	12 (80.0)	6 (66.7)	0.635
Endotracheal intubation	8 (53.3)	3 (33.3)	0.423
Central vascular catheter	7 (46.7)	2 (22.2)	0.389
Outcome			
Discharged	12 (80.0)	8 (88.9)	1.000
Died	3 (20.0)	1 (11.1)	1.000
Intensive care in ICU	11 (73.3%)	3 (33.3)	0.092

* Group 1, hvKP isolated from non-blood or abscess samples; ** Group 2, hvKP isolated from blood or abscess samples.

8.3%, cefazolin 20.8%, cefuroxime 20.8%, ceftriaxone 16.7%, ceftazidime 8.3%, cefepime 12.5%, aztreonam 12.5%, imipenem 8.3%, meropenem 8.3%, cefotetan 12.5%, levofloxacin 8.3%, ciprofloxacin 8.3%, gentamicin 4.2%, tobramycin 4.2%, amikacin 0%, nitrofurantoin 50.0% and trimethoprim-sulfamethoxazole 8.3%. hvKP isolated from two groups had similar drug resistant rates (Table 3). Resistance to imipenem and meropenem was observed in two isolates which were believed to cause hvKP-associated pneumonia.

Molecular characteristics of hvKP

Twenty-one of the 24 hvKP isolates obtained from infected patients were serotyped by PCR (Table 4). Three of the 24 were not typeable. Nine of 21 (42.3%)

Table 3. Antimicrobial resistance patterns.

Drug	No. of isolates resistant (%)			P Value
	Total (n = 24)	Group 1* (n = 15)	Group 2** (n = 9)	
Ampicillin	24 (100)	15 (100)	9 (100)	NA
Ampicillin-Sulbactam	5 (20.8)	5 (33.3)	0 (0)	0.118
Piperacillin	7 (29.2)	6 (40.0)	1 (11.1)	0.191
Piperacillin-Tazobactam	2 (8.3)	2 (13.3)	0 (0)	0.511
Cefazolin	5 (20.8)	4 (26.7)	1 (11.1)	0.615
Cefuroxime	5 (20.8)	4 (26.7)	1 (11.1)	0.614
Ceftriaxone	4 (16.7)	3 (20.0)	1 (11.1)	1.000
Ceftazidime	2 (8.3)	2 (13.3)	1 (11.1)	0.511
Cefepime	3 (12.5)	2 (13.3)	1 (11.1)	1.000
Aztreonam	3 (12.5)	2 (13.3)	1 (11.1)	1.000
Imipenem	2 (8.3)	2 (13.3)	0 (0)	0.511
Meropenem	2 (8.3)	2 (13.3)	0 (0)	0.511
Cefotetan	3 (12.5)	3 (20.0)	0 (0)	0.266
Levofloxacin	2 (8.3)	2 (13.3)	0 (0)	0.511
Ciprofloxacin	2 (8.3)	2 (13.3)	0 (0)	0.511
Gentamicin	1 (4.2)	1 (6.7)	0 (0)	1.000
Tobramycin	1 (4.2)	1 (6.7)	0 (0)	1.000
Amikacin	0 (0)	0 (0)	0 (0)	NA
Nitrofurantoin	12 (50.0)	9 (60.0)	3 (33.3)	0.400
Trimethoprim-Sulfamethoxazole	2 (8.3)	2 (13.3)	0 (0)	0.511

*Group 1, hvKP isolated from non-blood or abscess samples; **Group 2, hvKP isolated from blood or abscess samples; NA, not applicable.

Table 4. Distribution of clonal complexes (CCs), sequence type (ST), capsule serotypes (K type), pLVPK-derived loci *(terW-iutA-rmpA-silS*) and *repA*.

Isolate number	CCs	ST	K type	*ter*W	*iut*A	*rmp*A	*sil*S	*rep*A
13[a],14[c], 26[b],43[c]	cc23	23	1	+	+	+	+	
12[b]	cc23	23	1	+	+	+	+	+
18[c],48[c]	cc65	25	2	+	+	+	+	+
21[c]	cc65	25	2		+	+	+	
46[d]	cc65	65	2	+	+	+	+	+
36[a]	cc65	375	2		+	+	+	+
5[a],30[c],40[b]	cc86	86	2	+	+	+	+	+
23[a]	cc86	801	2	+	+	+	+	+
10[d]	cc29	29	54					
34[c]	cc29	29	54	+	+	+		
16[c]	singleton	485	5	+	+	+		+
25[a]	singleton	893	20	+	+	+	+	
3[c]	singleton	412	57	+	+	+	+	
38[c]	singleton	412	57	+	+	+	+	
17[c]	singleton	412	57	+	+	+		
24[d]	singleton	40	N					
11[d]	singleton	91	N	+	+			
9[a]	singleton	692	N			+		

a, isolated from abscess; b, isolated from blood; c, isolated from tracheal secretions; d, isolated from urine; N, non-typable, unidentified serotype.

Table 5. Capsule serotypes (K type), clonal complexes (CCs) and virulent genes of hvKP isolates.

K type, CCs and virulent genes	Groups, n (%)		
	Group 1 (*n* = 15)	Group 2 (*n* = 9)	*p* value
k1^{CC23}	2 (13.3)	3 (33.3)	0.326
k2^{CC86} and k2^{CC65}	5 (33.3)	4 (44.4)	0.678
k2^{CC86}	1 (20.0%)	3 (75.0)	0.206
k2^{CC65}	4 (80.)	1 (25.0)	0.203
non K1/K2 (CC29 and singletons)	8 (53.)	2 (22.2)	0.210
uge	12 (80.0)	9 (100%)	0.266
wabG	14 (93.3)	9 (100)	1.000
fimH [c]	1 (6.7)	9 (100)	0.000
ycfM [c]	2 (13.3)	9 (100)	0.000
entB	15 (100)	9 (100)	NA
ureA	14 (93.3)	9 (10)	1.000
iroN	14 (93.3)	9 (100)	1.000
mrkD	12 (80.0)	8 (88.9)	1.000
kfuBC	2 (13.3)	1 (11.1)	1.000
cf29a	1 (6.7)	2 (22.2)	0.533
alls	4 (26.7)	3 (33.3)	1.000
ybtS	7 (46.7)	7 (77.8)	0.210
terW^{+}-iutA^{+}-rmpA^{+}-silS^{+}	8 (53.3)	7 (77.8)	0.389
terW^{+}-iutA^{+}-rmpA^{+}-silS^{+}-repA^{+}	4 (26.7)	4 (44.4)	0.412

Group 1, hvKP isolated from non-blood/abscess samples; Group 2, hvKP isolated from blood or abscess samples; NA, not available.

isolates were serotype K2, including 3 of 6 abscess, 1 of 3 blood, 4 of 11 tracheal secretion and 1 of 4 urine isolates. K1 was the second most common serotype, present in 3 of 6 blood and 2 of 11 tracheal secretion isolates. Serotype K20 and K5 was observed in 1 hvKP abscess isolate.

Thirteen sequence types (STs) were identified in the 24 hvKP isolates (Table 4). All K1 strains were ST23 (n = 5). There were 5 STs among the nine K2 isolates, ST65 (n = 1), ST86 (n = 3), ST25 (n = 3), ST375 (n = 1), and ST801 (n = 1). Seven STs were found in the 14 non-K1/K2 isolates. Cluster analysis with eBURST grouped the 13 STs into 4 CCs and 6 singletons. Correlations between CCs and K serotype were found. All the K1 strains belong to CC23 (5/24, 20.8%) and all the K2 strains belong to CC86 (4/24, 16.7%) and CC65 (5/24, 20.8%). There was no statistical difference in the distribution of the capsular serotypes between group 1 and group 2 (Table 5).

The virulence genes *mrkD*, *kfuBC*, *cf29a*, *uge*, *wabG*, *ureA*, *ybtS*, *IroN*, *allS,* and pLVPK-derived genetic loci were evenly distributed between the two groups (Table 5). *fimH* and *ycfM* were more frequently expressed in group 2 ($p < 0.0001$).

Discussion

All hvKP isolates obtained from a large urban hospital during two years were evaluated in our laboratory. The infrequency of this infection led to the identification of only 24 hvKP isolates from 24 patients during a 2-year period. hvKP isolates comprised 7.5% of all KP isolates from our hospital, 60% of which were associated with infection. We identified hvKP more frequently in urine and abscess, and less frequently in blood, tracheal secretion, and bile than another similar large hospital in China [26]. Most community-acquired infections were blood infections or a presence of different abscess, similar to previous reports [12, 16, 27]. Out of all, 40% (6/15) hvKP infections in non-blood/abscess group were defined as hospital-acquired versus 11.1% (1/9) in blood/abscess group. This may suggest an elevated risk for hospitalized patients and the potential dissemination of hvKP strains in health care facilities.

Colonization with hvKP is thought to be a first step in developing infection [28]. Patients with pyogenic liver abscesses have been reported to have frequent intestinal (81.4%) and/or pharyngeal (39.5%) colonization with hvKP [29]. We found hvKP colonization in 16 patients. Colonized fluids included tracheal secretions, urine and superficial secretions. Factors leading from colonization to infection are not well understood [8]. The presence of hvKP in the urine may be a potential marker for bacteremia [18]. Therefore, at the time of hvKP isolation, strict adherence to standard hospital infection control precautions should be reinforced to limit its spread.

The hvKP that we evaluated had similar antibiotic resistance patterns as previous reports. An exception to this finding was the presence of carbapenem resistance

identified in hvKP isolated from tracheal secretions and urine of patients in Group 1 [12, 26]. These two isolates were characterized as K2/ST25 and K2/ST65 with bla_{KPC-2}, respectively. The study from China revealed 5 K1 cr-hvKP isolates with plasmid-borne blaKPC-2 gene and genetic relation between 3 of them [30]. The development of resistant strains of hvKP demonstrates a need for avoiding unnecessary antibiotic use that stimulates the generation of resistant strains. This problem is emphasized by a cr-hvKP isolate obtained from an elderly man receiving chemotherapy who was previously treated because of another systemic infection before developing a fatal cr-hvKP infection [31].

The bacterial capsule is an important virulence factor and serotypes K1 and K2 have been particularly linked to severe bacteraemia and liver abscess [32, 33]. These findings have rarely been reported in fluids other than blood and /abscess. In the present study, no difference was found in the distribution of capsular serotypes of blood/abscess and non-blood/abscess groups.

K. pneumoniae virulence determinant pLVPK is a 219,385-bp plasmid isolated from the invasive K2 strain CG43. pLVPK-derived *terW-rmpA-iutA-silS* loci are independent pathogenicity factors for abscess formation [25]. pLVPK derivatives could be extrachromosomal and carry the *repA* gene, or be a chromosome-integrated form [25, 34]. Gene deficiency of pLVPK derivatives was found for the first time in the hvKP isolates except K1 type. *entB, iroN, ybtS, kfuBC*, and *iutA* are part of iron scavenging systems that contribute to bacterial virulence [18]. Similar expression patterns were found in both groups. Both, *fimH*, which encodes type 1 fimbriae adhesion and *ycfM,* which encodes an outer membrane lipoprotein, were more common in group 2 and could also contribute to bacterial virulence.

There were several limitations to this study. The small number of hvKP isolates obtained does not support subgroup analyses. Not all patients were tested for colonization at admission and there was limited testing of colonization sites. The use of 48 hours as a cut-off for diagnosing nosocomial infections was arbitrary and could led to an overestimation of nosocomial infections. However, the frequency of community acquired hvKP infections in our patients was similar to that reported from other centers [26].

Conclusions

This study is unique in comparing the clinical and microbiological characteristics of hvKP isolates obtained from blood and abscess to those obtained from other fluids. Bacteria isolated from all areas had similar clinical characteristics and virulence characteristics. Antibiotic resistance is a developing problem with hvKP.

Acknowledgements

We thank XiaoWei Zhang and Lei Zhou for their assistance in laboratory work. This work was supported for Xiumei Xiao by Scientific Research Foundation for the Returned Overseas Scholars, Peking University Third Hospital (grant reference: 79482-2).

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Corresponding author

Prof. J. Zhang
Department of Laboratory Medicine, Peking University Third Hospital, No. 49 North Garden Road, Haidian District, Beijing 100191, China
Phone: 86-10-82266249
Fax: 86-10-82267616
Email: zhangjiebjmu15@163.com

Conflict of interests: No conflict of interests is declared.