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Clinical challenges with hypervirulent *Klebsiella pneumoniae* (hvKP) in China

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ABSTRACT

Hypervirulent *Klebsiella pneumoniae* (hvKp) is an evolving pathotype with higher virulence than classical *K. pneumoniae* (cKp) and is characterized by community-acquired, multiple sites of infections and young and healthy hosts. hvKP infections were primarily found in East Asia and have been increasingly reported worldwide over the past few decades. To better understand the clinical challenges faced by China with hvKP, this review will provide a summary and discussion focused on recognizing hvKP strains and prevalence of antibiotic-resistant hypervirulent strains in China and the mechanisms of acquiring antimicrobial resistance. Compared with cKP, hvKP is likely to cause serious disseminated infections, leading to a higher mortality. However, sensitive and specific clinical microbiology laboratory tests are still not available. Given the limited published data due to the clinical difficulty in differentiating hvKP from cKP, extrapolation of the previous data may not be applicable for the management of hvKP. A consensus definition of hvKP is needed. Furthermore, an increasing number of reports have described hvKp strains with antimicrobial resistance acquisition, increasing the challenges for management of hvKP. China, as an epidemic country, is also facing these challenges. Quite a number of studies from China have reported antibiotic-resistant hvKP strains, including extended-spectrum β-lactamase (ESBL), and carbapenem-, tigecycline-, and colistin-resistant strains. hvKP infections, especially those of antimicrobial-resistant strains, pose to be a great threat for public health in China. Therefore, an immediate response to recognize the hypervirulent strains and provide optimal treatments, especially those with resistance determinants, is an urgent priority for China.

Key words: hypervirulent *Klebsiella pneumoniae*, antimicrobial resistance, acquisition, resistance mechanism

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INTRODUCTION

Klebsiella pneumoniae is one of the most relevant pathogens causing community-acquired and nosocomial infections in immunocompromised individuals, including pneumonias, urinary tract infections, bacteremias, and liver abscesses. Hypervirulent *K. pneumoniae* (hvKP) was firstly reported in the mid-1980s and was found to cause serious disseminated infections in young and healthy individuals.[1,2] hvKP infections were primarily found in East Asia and are now increasingly being reported worldwide over the past few years, which has been a concern because the hvKP strains are life-threatening in young and healthy individuals.[1,3] Colonization rates of *K. pneumoniae* in feces from healthy adults were 87.7%, 61.1%, 75%, 57.9%, 18.8%, 52.9%, and 41.3% for Malaysia, Singapore, Taiwan, mainland China, Japan, Thailand, and Vietnam, respectively.[4,5] Also, colonization rates of hvKP were 14.1%, 14.9%, 11.3%, 11.7%, 16.7%, and 2.7% for Malaysia, Singapore, Taiwan, mainland China, Japan, and Thailand, respectively.[5] The prevalence of hvKP infections ranged from 8.33% to 73.9% in China.[1] Compared with cKP, hvKP is more likely to cause a higher mortality.[6] hvKP is susceptible to the commonly

Table 1. Epidemiology of antibiotic-resistant hvKP in mainland China

Site	Time frame	Isolate source/ characteristic	Number	ST	Capsule type	Resistant mechanism	Reference
Hangzhou	2016	Sputum/CR	5	ST11	K47	*bla*KPC□2	7
Hangzhou	2016	Feces/colistin-resistant	1	ST661	K1	*mcr-1*	8
Sichuan	2018	Sputum/CR	1	ST29	K54	*bla*NDM-5	9
ShenZhen	2018	Feces/MDR (penicillin, quinolone, carbapenem -resistant)	1	ST23	K1	*bla*SHV-190 *oqxAB*,*bla*VIM-1	10
Wenzhou	2017-2018	Sputum, fecal, UT, blood/CR	29	ST11, ST37, ST375	K2	*bla*KPC□2	11
Beijing	2017-2018	Sputum/CR	7	ST17, ST23, ST347, ST412, ST2874	indeterminate	indeterminate	12
		Sputum/ESBL	13	indeterminate	indeterminate	indeterminate	
Changsha	2014-2017	Sputum/CR	20	ST25, ST11 and ST375	K2	*bla*KPC-2, *bla*NDM-1	13
Sichuan	2015-2016	Blood/Colistin-resistant	5	ST23, ST700, ST660, ST412	K1, K16, K57	*mcr-1, PhoQ, D150G*	14
Nanchang	2017	Sputum, pus, blood, UT/Quinolone resistant	18	ST23	K1	*qnrS1, aac(6')-Ib-cr, qnrB4*	15
Nanchang	2017-2018	Blood, sputum, pus, UT/CR	39	indeterminate	indeterminate	*bla*KPC-2 , *bla*NDM-1	16
		ESBL	35	indeterminate	indeterminate	*ESBL*(*bla*SHV-1, *bla*TEM-1, *bla*CTX-M-14)	
Hangzhou	2018	Vitreous fluid/ESBL	1	ST2922	K1	*blaCTX-M-14*	17
Wuhan, Zhejiang, *etc*.	2013	Sputum, blood, abdomine/ESBL	11	ST17, ST23, ST35, ST65, ST268, ST367, ST420, ST1658	K1,K2,K20	*ESBL*	1

hvKP: hypervirulent Klebsiella pneumoniae; ESBL: extended-spectrum-β-lactamase; CR: carbapenem-resistant*; MDR: multidrug resistant; ST: sequence type; UT: Urinary tract.*

used antimicrobial agents, except that it has an intrinsic resistance to ampicillin.[2] However, previous reports have demonstrated that antibiotic-resistant hvKP isolates are increasing, including carbapenem-resistant, extended-spectrum b-lactamase (ESBL) and colistin-resistant hvKP strains (Table 1).[1,7–17] Antibiotic-resistant hvKP strains, such as carbapenem-resistant hvKP (CR-hvKP) strains, may cause severe infections in healthy individuals and they are a great threat to public health. Besides, the mechanisms of acquiring antimicrobial resistance for hvKP strains are variable.[4] Identifying the hypervirulent strain immediately and providing optimal treatments, especially those with resistance determinants, is of great importance, especially for China which has a high prevalence of hvKP infections. However, a consensus definition of hvKp in clinical practice is still not available because of the difficulties to distinguish an hvKP strain from a cKP strain. There are clinical challenges involved with hvKP in China, including early recognition and appropriate treatment. Therefore, in this review, we summarize the epidemiology of hvKP isolates and antibiotic-resistant hvKP isolates in China and discuss the clinical characteristics, laboratory tests for hvKP, and the resistance mechanisms involved.

CHALLENGE FOR RECOGNIZING AN HVKP STRAIN IN CLINICAL PRACTICE

The prevalence of hvKP infection varied in different regions of mainland China, with the highest rate (73.9%) found in Wuhan.[1] In another study, 22.8% (84/369) of *K. pneumoniae* clinical isolates associated with invasive infections in China were identified as hvKP.[2,18] Compared with cKP strains, hvKP is likely to cause disseminated invasive infections, leading to a higher mortality. As a consensus definition of hvKp in clinical practice is still not available, studies published previously used various criteria to define these strains, such as the

string test and aerobactin test, increasing the challenges for clinicians to identify hvKP, interpret, and compare the data.[1,2,18,19] Suspicion of a clinician is the only means by which hvKp would be diagnosed. hvKP is characterized by metastatic invasive and community-acquired infection and young, healthy hosts. Liu et al revealed a high prevalence (45.7%) of hvKP in elderly patients in China.[20] Therefore, clinical criteria are problematic. As for the clinical microbiology laboratory tests to distinguish hvKp from cKp, the string test was primarily used to identified hvKP strains, but later proved to be nonspecific.[1] However, owing to the lack of a sensitive and specific clinical laboratory test for hvKP strains, there are still studies confirming hvKP based on the string test, which may cause confusion for clinicians.[2,18,21] Identification of hvKp as the infecting agent is important. The genetic determinants of hypervirulence are found on large virulence plasmids as well as chromosomal mobile genetic elements, which can be used as biomarkers to distinguish hvKp from cKp clinical isolates.[2] Studies have been published on hypervirulence-associated factors in hvKP strains, including capsular serotype, sequence type (ST), virulence plasmid, etc.[1,19,20] Results of previous studies have demonstrated that peg-344, iroB, iucA, prmpA, prmpA2, and siderophore production greater than 30 μg/ml could be used to differentiate hvKp from cKp strains accurately.[19] Russo et al considered that total siderophore production, or iuc and/or either rmpA or rmpA2 could be the most accurate and durable marker.[22] These findings provided possible genotype or phenotype biomarkers for the diagnosis of hvKP. There is still a long way to go for these genetic determinants of hypervirulence to become commercially available for clinical laboratory tests. Distinguishing an hvKP strain from cKP is still a challenge for clinicians when hvKP is suspected.

CHALLENGE WITH ANTIBIOTIC-RESISTANT HVKP

Most hvKP strains are rarely resistant to commonly used antimicrobial drugs.[2] However, reports of antibiotic-resistant hvKP isolates have been increasing over the past few years, mostly in countries with an epidemic dissemination of hvKP, including China (Table 1).[1,2,7–17] China is facing the challenge of increasing antibiotic-resistant hvKp strains, which is a real threat for public health. In one investigation from China, 37% (85/230) of *K. pneumoniae* clinical isolates were identified as hvKp strains based on the presence of *rmpA*, and 13% of these produced ESBL.[1] Gu et al reported an outbreak of CR-hvKP from five patients in China; all the five representative CR-hvKP strains belonged to the ST11 type, which is the most prevalent ST associated with CR-hvKP in China.[7] Also, the team firstly reported the emergence of colistin- and CR-hvKP strains through complete sequence analysis of ST11 CR-hvKP and proposed the probable mechanisms of transmission of virulence plasmids from ST23 hvKP to ST11 CR-KP. [23] Feng et al reported emergence of CR-hvKP of ST36.[24] Li et al found two hvKP strains were not susceptible to tigecycline.[13] Cheng et al reported six tigecycline-nonsusceptible hvKP strains in their study.[25] Huang et al reported emergence of an extreme drug-resistant (XDR) and carbapenemase-producing hvKP strain which was resistant to tigecycline and colistin, in addition to carbapenems.[26] Twenty-six hvKP strains in this study were firstly reported to co-carry carbapenemase genes, ESBL genes, quinolone resistance genes, and 16S rRNA methylase genes simultaneously.[16] These strains are not only hypervirulent and multidrug resistant (MDR), but also highly transmissible, causing severe and fatal infections in both hospital settings and the community.

It is well known that the virulence genes of an hvKP strain are located on either the chromosome or the virulence plasmid. Based on previous studies, several mechanisms of acquisition of antimicrobial resistance of hvKP have been proposed, which can occur variably.[4] The first is that a conjugal plasmid with antimicrobial resistance determinants is acquired by an hvKp strain.[24,27] The second mechanism is acquisition and integration of an integrative conjugative element (ICE) containing antimicrobial resistance determinants into an hvKp strain.[28,29] The third mechanism is disruption or mutations in chromosomal genes.[23] The fourth is acquisition of the hvKp virulence plasmid by MDR or XDR cKp strains.[4] Dong et al demonstrated that K1 hvKP strains were capable of acquiring a plasmid harboring the bla_{KPC-2} gene, or by incorporating a mobile bla_{KPC-2}-bearing DNA fragment into the virulence plasmid, suggesting the possibility of initial integration of these extrachromosomal elements, subsequent transfer, and resolution.[23] Emergence of antimicrobial resistance of hvKP increases difficulties for management of hvKP infection, inducing a lack of optimal treatments for antimicrobial-resistant hvKP. Besides, as hvKP strains can undergo nosocomial dissemination and are transmissible in the hospital setting, caution should be exercised to prevent and control hvKP infection in clinical practice. Management of hvKP infections a great challenge for clinicians.

CONCLUSION

hvKP infections have been increasingly reported worldwide, mainly along the epidemic countries in Asia, including China. Compared with cKP, hvKP has several characteristics, but they are not specific. Distinguishing hvKP strains from cKP strains in clinical practice is still

difficult. Reports of antibiotic-resistant hvKP isolates are increasing worldwide, including in China. Antibiotic-resistant hvKP strains including ESBL, carbapenem-resistant, and colistin-resistant hvKP strains have been found from China. These hypervirulent, multidrug resistant strains are a great threat for public health. Recognizing the hvKP strain earlier, providing appropriate treatments for hvKP infections, especially for antibiotic-resistant hvKP strains, preventing hvKP infections, and decreasing the rate of acquiring antimicrobial resistance for hvKP strains are the challenges faced by China.

Conflict of Interest

None declared.

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Nil

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