高毒力肺炎克雷伯菌耐药机制研究进展

车皓月[1]，胡波[2]，蔡芸[1*]，王睿[1]（1. 解放军总医院第一医学中心医保部药学部药物临床研究中心，北京 100853；2. 解放军总医院第一医学中心医保部药学部药品供应中心，北京 100853）

摘要：肺炎克雷伯菌（*Klebsiella pneumoniae*, KP）是院内感染的常见革兰阴性致病菌；20 世纪 80 年代以来，KP 的一种新型变异株 – 高毒力肺炎克雷伯菌（hypervirulent *K. pneumoniae*, hvKP）不断产生和蔓延，常感染健康宿主并引起严重的侵袭性感染；早期研究认为高毒力与耐药性不会在同一 KP 出现，但近期已有 hvKP 相关菌株耐药甚至多药耐药的报道，耐药性和高毒力的结合可能会成为下一个临床即将面临的重要挑战。现就 hvKP 耐药报道及相关机制研究进行综述和讨论，希望能为预防和控制耐药 hvKP 在我国的流行和发展以及为进一步对耐药机制进行深入研究提供参考。

关键词：肺炎克雷伯菌；高毒力；耐药性；遗传学

中图分类号：R978.1 **文献标识码：**A **文章编号：**1002-7777(2019)02-0195-07
doi:10.16153/j.1002-7777.2019.02.013

Research Progress of Resistance Mechanism of Hypervirulent *Klebsiella Pneumoniae*

Che Haoyue[1], Hu Bo[2], Cai Yun[1*], Wang Rui[1] (1. Center of Medicine Clinical Research, Department of Pharmacy, PLA General Hospital, Beijing 100853, China; 2. Center of Drug supply, Department of Pharmacy, PLA General Hospital, Beijing 100853, China)

Abstract: *Klebsiella pneumonia* (KP) is a common gram negative pathogen of hospital-acquired infections. A new variant of KP called hypervirulent *K. pneumoniae* (hvKP) has been gradually produced and spread since the 1980s and often infects healthy hosts and causes serious invasive infections. Early studies have suggested that the high virulence and drug resistance of KP did not overlap, but recently there are reports of drug resistance or even multidrug resistance of hvKP-related strains. Combination of drug resistance and high virulence may become the next important challenge encountered in clinical practice. This paper reviews and discusses some hvKP drug resistance reports and related mechanism in order to provide references for the prevention and control of the prevalence and development of drug-resistant hvKP and further research on drug resistance mechanism in China.

Keywords: *Klebsiella pneumoniae*; high virulence; drug resistance; genetics

肺炎克雷伯菌（*Klebsiella pneumoniae*, KP）是医院获得性感染的常见致病菌，多发生于医院或长期护理机构中的合并多种疾病患者[1]。KP常被分为两类，一种为经典肺炎克雷伯菌（classic *Klebsiella pneumoniae*, cKP），是引起医院获得性感染的常见病原体，其多药耐药（multidrug-resistant, MDR）

基金项目：国家自然基金面上项目（编号 81573472，编号 81770004）
作者简介：车皓月，在读硕士研究生；研究方向：抗感染药物合理应用；E-mail：mydreamishappy@yeah.net
通信作者：蔡芸，副研究员；研究方向：抗感染药物临床药理学；E-mail：caicai_ai_hh@126.com

甚至广泛耐药（extensively drug-resistant, XDR）菌株给临床带来极大危害，可造成多系统感染，如肺炎、尿路感染、败血症、细菌性脑膜炎、心内膜炎手术伤口或其他伤口感染等[2]，而侵入性操作则是cKP常见的易感性因素之一。据统计，克雷伯菌属是中心静脉导管相关血流感染、导尿管相关泌尿系统感染、呼吸机相关肺炎和手术部位感染的第三常见病原体[3]。另一种为新型肺炎克雷伯菌变种，称为高毒力肺炎克雷伯菌（hypervirulent *K. pneumoniae*, hvKP），与cKP相比，hvKP能够导致更严重和散播性更强的感染，常见于肝脓肿，有时并发眼内炎和脑膜炎，也有其他侵袭性感染报道，包括骨髓炎和坏死性筋膜炎[4]。不同于cKP的是，hvKP感染患者通常没有侵入性治疗史[5]。作为能够在健康、活动个体中引起严重感染的超毒力病原体，hvKP的快速发展和传播成为目前临床关注的热点。本文将从hvKP的相关特点和耐药两个方面对hvKP的流行现状、分子特点、耐药现状以及相关机制进行综述，以期为耐药hvKP的预防和控制及深入研究提供参考。

1 hvKP的定义、流行现状、毒力因子、血清分型及遗传特点

1.1 定义及流行现状

hvKP是指最初从荚膜血清型K1或者K2中分离出来的、具有高侵袭性、常导致化脓性肝脓肿的一种社区获得性肺炎克雷伯菌[6]。在20世纪80年代，中国台湾地区首次发布了1例病例报告，详细描述了hvKP导致健康人罹患社区获得性肝脓肿并伴发严重的末端器官表现，如脑膜炎、眼内炎等[7-8]。此后，在欧洲、亚洲以及美洲都陆续报道了hvKP的传播，其中以亚洲的报道最多[9]。2016年，Guo Y等[10]报道的针对中国一家医院各类型的侵袭性感染相关的KP临床分离株中，有22.8%（84/369）为hvKP。另一项纳入中国10个城市共230株KPs的研究[11]显示，有37.8%为hvKP，且hvKP菌株具有地区分布差异，武汉地区最高（73.9%），浙江诸市最低（8.3%）。引起化脓性肝脓肿的KP病原体研究发现，90.9%（40/44）为hvKP[12]。除中国外，亚洲其他国家如韩国、伊朗等地区也有相关报道[9,13]。与亚洲所报道的较高hvKP发生率相比，其他地区如西班牙、加拿大等地肺炎克雷伯菌中分离出的高毒性克隆株并不常见[14-15]。

1.2 毒力因子

传统上普遍认为hvKP与cKP相比，其主要特点之一就是高黏度（Hyperviscous），也是hvKP能在无侵入性治疗史的健康宿主中造成侵袭性感染的主要原因。临床上常用拉丝实验作为半定量测量方法结合临床症状（是否发生侵袭性感染）辅助确诊hvKP[16]。高黏度的产生原因是荚膜多糖（Capsular polysaccharides, CPS）的过度分泌[17]，因此，CPS被认为是hvKP重要的毒力因子。KP的CPS至少可分为78种血清型，其中，K1和K2荚膜血清型与hvKP密切相关[6,9]，其他在hvKP菌株中被检出的荚膜血清型还有K5、K20、K54和K57[18]，但检出率相对较低。虽然，目前临床分离出的hvKP大多数具有高黏度表型，但近年来，逐渐有一些具有高黏度表型而聚合酶链反应（polymerase chain reaction, PCR）却检测不到毒力因子表达的克雷伯氏菌株被分离出来[19]；同时，也发现部分菌株不表达高黏度表型，但是却在健康人群中引起侵袭性感染[14]，说明高毒力和高黏度表型不具备同一性。Qiucheng Shi等[20]收集56株hvKP分离株，通过拉丝实验测定黏度表型，发现高毒力组和中毒力组之间黏度表型并无显著性差异，因此，认为拉丝实验并不能作为评估肺炎克雷伯菌毒力的灵敏方法。

此外，铁摄取系统也是目前研究较多的hvKP毒力因子。目前，报道的与毒力密切相关的铁载体包括岐杆菌素、肠杆菌素、沙门菌素和耶尔森菌素等[21]，是微生物分泌的低分子量、高亲和力铁螯合化合物，能高度亲和可溶性三价铁离子，是使KP能够在低铁浓度培养基中存活的重要代谢物，同时，也能吸附并溶解宿主转铁蛋白中的铁，促进自身生长繁殖的同时实现毒力作用[22]。hvKP比cKP菌株在数量上能产生更多的类铁蛋白，这些类铁蛋白在生物学上更加活跃，即对铁的亲和力增强或对宿主因子的抵抗力增强[23]。

1.3 遗传特点

与cKP相比，hvKP分离株大多属于K1、K2血清型，此外，与hvKP毒力密切相关的基因还有*rmpA*、*uge*、*kfu*、*magA*等[24-25]。使用基因多位点序列分析（multilocus sequence analysis, MLSA）或者全基因测序对不同的hvKP菌株进行基因测序，发现测得K1 hvKP菌株的基因序列绝大多数属于同一个克隆复合体-CC23（clonal complex 23），且

CC23谱系具有同源性[6]，与特定毒力因子相关[26]。而K2血清型的分离株在遗传上则具有更加多样性和分散性，目前，已经测得序列型（Sequence-typying, STs）包括ST65、ST66、ST86、ST373、ST374、ST375、ST380、ST434等[26-27]。

2 hvKP的耐药现状及机制

KP是全球抗生素耐药性产生的主要承载体，几乎所有的KP菌株中都含有承载耐药相关遗传信息的质粒，且耐药性KP菌株的流行呈现多样化和全球化的趋势[28]。与耐药cKP的高流行性相比，hvKP的耐药情况相对较少[17]，高毒力与耐药性曾被认为不重叠出现[29]。然而近年来，在世界范围内，特别是在亚洲的一些hvKP流行国家，关于耐抗菌药物的hvKP分离株报道越来越多。尤其是hvKP获得性碳青霉烯耐药，正在对我国的hvKP临床用药造成威胁。耐药性以及高毒力的重叠将会给临床治疗带来不可预期的危害。Shon AS等[1]预测hvKP超毒力和广泛耐药可能会趋同，使药物治疗变得越来越难，如果不加以干预，hvKP将会是接下来的“超级细菌”。

2.1 碳青霉烯耐药

目前，关于hvKP耐药的报道中，碳青霉烯类耐药相关的占多数，产肺炎克雷伯菌碳青霉烯酶（*Klebsiella Pneumoniae* Carbapenemase, KPC）是碳青霉烯类耐药的主要机制，而肺炎克雷伯菌也是KPC基因最常见的载体[30]。Bei Yao等[18]对某三级医院4例耐碳青霉烯类高毒力克雷伯菌（carbapenem-resistant hypervirulent *Klebsiella pneumoniae*, cr-hvKP）和29例耐碳青霉烯类经典克雷伯菌（carbapenem-resistant classic K. pneumonia, cr-cKP）进行回顾性分析发现，所收集的cr-hvKPs共属于3种序列型（ST25、ST65、ST11），绝大多数cr-hvKPs均检测到*KPC-2*基因，且与cr-cKPs相比，pLVPK相关基因位点、*rmpA*、*iroN*和K2血清型在cr-hvKPs中表达更为普遍。此外，Jane F. Turton等[31]也检测到了KPC基因阳性的高毒性K1-ST23分离株；ST11是中国最常见的cr-cKPs基因序列型，在中国某医院就发生了一次ST11 cr-hvKP致命的爆发性流行，共感染5例患者。基因组分析表明，ST11 cr-hvKP的出现是由于cr-cKPs获得了大约170 Kbp的*pLVPK*样毒力质粒[32]，提示cKP和hvKP菌株之间质粒介导的耐药基因水平传播的可能性。在浙江，则发现了5株通过手术伤口感染的K1 hvKPs，其中包括新的序列型ST1797，并且，所有菌株都携带*magA*和*wcaG*毒力基因，以及质粒携带的bla_{KPC-2}基因[33]，类似全国范围内报告的同样携带bla_{KPC-2}基因并表现高毒力的新序列型还有ST36[34]。cr-hvKP分离株不仅在中国等hvKP高发地区有报道，Mohammad Ali Tabrizi A等[35]近期也首次在伊朗医院ICU机械通气病人的气管标本中发现cr-hvKP分离株，经鉴定为K1-ST23序列类型，携带有bla_{VIM-2}基因，位于Ⅰ型整合子上，提示在hvKP中携带bla_{VIM-2}偶联质粒可能是由通过水平基因转移获得，并在菌株之间扩增。此外，英国一家医院也首次检测到K1-ST23 hvKP，属于CC23，分离株可见bla_{NDM}基因阳性[36]。

2.2 β-内酰胺类耐药

超广谱β-内酰胺酶（Extended-Spectrum β-Lactamases, ESBL）是目前已知细菌对β-内酰胺类抗菌药物产生耐药的主要机制。目前，关于hvKP针对β-内酰胺类抗生素耐药的报道相对较少，且主要围绕产ESBL的 hvKPs展开，有报道称ESBL在cKPs中的发生率明显要高于hvKPs[37]。一项针对中国hvKPs抗菌药物的耐药性研究显示，收集的230株hvKPs数据信息中有12.6%的hvKP分离株ESBLs阳性，其中大部分携带bla_{CTX-M}基因，且中性粒细胞减少患者、系统性类固醇治疗史和联合治疗更容易感染产ESBL hvKP[11]。国内类似的研究还有针对北京朝阳医院的70例菌血症患者进行的回顾性分析，其中有31.4%的患者发现hvKP，确定了两株产ESBL hvKP菌株[38]，以及北京佑安医院的29例hvKP确诊患者，其中17%表达ESBL[39]。Khalit S. Khaertynov等[40]近期报道了1例产ESBL hvKP感染脑膜炎的新生儿病例，该菌株对氨基青霉素和三代头孢耐药，但对亚胺培南和美罗培南敏感，预后不良。Yan. Q等[41]对2014年1月-12月的49例机械通气患者KP感染进行回顾性研究时，发现1株产ESBL hvKP，鉴定为K54 ST29序列类型。此外，在法国也报告了1例hvKP，通过克拉维酸与三代头孢和氨曲南的双纸片协同试验（Double-disk synergy test, DDS）鉴定了产ESBL表型，且对第三代头孢菌素和除阿米卡星以外的所有氨基糖苷高度耐药[42]；Chaitra ShanKar等[43]报告了从一名感染败血症的新生儿中分离出的产ESBL hvKP菌株，并对其遗传信

息进行鉴定，发现其属于新序列型ST2318。

2.3 多粘菌素耐药、多药耐药和泛耐药

多粘菌素是治疗多药耐药革兰阴性菌感染的最后防线[44-45]，起初关于其耐药的报道较少，但由于多药耐药革兰阴性菌的泛滥，2000-2010年多粘菌素消耗量剧增[46]，不可避免地导致了多粘菌素相关耐药性的产生。质粒介导的多粘菌素耐药基因*mcr-1*是细菌对多粘菌素产生抗性的重要遗传机制之一，它的出现提示对其引起耐药性需要加以关注[47]。Danxia Gu等[48]报告了1例从中国婴儿患者中检测到的携带*mcr-1*的hvKP分离株的案例；Choi.MJ等[49]在一项多粘菌素耐药性与ST23 hvKP菌株毒力和适应性交互作用的研究中，从3株多粘菌素敏感的ST23 hvKP菌株中筛选出了多粘菌素耐药突变体，并证实了在hvKP多粘菌素耐药性的获得会伴随CPS产生减少、毒力及适应性减弱，也在一定程度上佐证了耐药hvKP低流行性的原因。此外，在巴西，也发现了多株对多粘菌素表现出高抗性的高粘液表型KP，并且同时检测出了相关毒力因子的基因编码[50]。

随着hvKP耐药菌株的不断出现以及抗菌药物的治疗应用， MDR甚至XDR产生是必然趋势，也是令人最为担心的公共卫生问题。MagioraKos等[51]专家于2012年在《Clinical Microbiology and Infection》杂志上正式发表MDR、XDR耐药菌暂行标准定义，列举了16类抗菌药物用于定义肠杆菌科MDR、XDR。临床上多粘菌素和替加环素通常对MDR或XDR革兰阴性菌(包括产碳青霉烯酶)敏感，常作为有效的抗MDR、XDR肺炎克雷伯菌的活性抗菌药物[52]。Huang.YH等[53]从腹腔内脓肿病例中分离出了一株包含*rmpA*和*rmpA2*基因和*KPC-2*基因的XDR ST11 hvKP菌株，除碳青霉烯外，对多粘菌素和替加环素均耐药，且在小鼠致死性试验中表现为体内高毒力。圣保罗大学微生物学系[54]提供了1例MDR hvKP的基因序列草图，血清型为K19，属于ST29序列型，携带包括$bla_{CTX-M-15}$在内的多种耐药基因以及毒力基因。巴西的一项筛选出抗多粘菌素的hvKP报告中[50]，描述了一种毒性强、广泛耐药（包括多粘菌素B耐药）、携带*QnrS-1*、*CTX-M-2*和*KPC-2*基因的ST11国际高危克隆株的扩展和进化[50]，Goncalves.GB等[55]也对巴西的MDR hvKP菌株的传播有所描述。

3 结语

随着hvKP耐药菌株不断涌现，相关的致死性病例报道也越来越多。虽然目前尚未出现大范围的hvKP耐药菌株流行，但如果不及时加以预防和控制，耐药hvKP将不可避免的成为下一个“超级细菌”。对于hvKP菌株耐药相关的机制研究仍处于起步阶段，包括毒力、耐药决定因素、遗传谱系相关信息、转移扩散机制、有效诊断识别工具以及潜在的抗菌靶标和防治措施等均有待于深入研究。总之，hvKP耐药菌株的出现具有警告意义，尤其是我国作为hvKP高发地区，在实施严格的防控措施的同时，需要投入更多的研究。

参考文献：

[1] Shon.Russo. Hypervirulent Klebsiella Pneumoniae: The Next Superbug?[J]. Future Microbiology，2012，7（6）：669-671.

[2] Akova.Daikos, Tzouvelekis. Interventional Strategies and Current Clinical Experience with Carbapenemase-producing Gram-negative Bacteria[J]. Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 2012，18（5）：439-448.

[3] Calfee DP. Recent Advances in the Understanding and Management of Klebsiella Pneumoniae[J]. F1000Res，2017，254（9）：187-192.

[4] Harada.Doi. Hypervirulent Klebsiella Pneumoniae: a Call for Consensus Definition and International Collaboration[J]. Journal of Clinical Microbiology，2018，56（9）：131-153.

[5] Wu.Li, Zhou. Bacteremia and Other Body Site Infection Caused by Hypervirulent and Classic Klebsiella Pneumoniae[J]. Microbial Pathogenesis，2017，55（8）：254-262.

[6] Struve Roe.Stegger. Mapping the Evolution of Hypervirulent Klebsiella Pneumoniae[J]. mBio，2015，6（4）：16-13.

[7] Chiu, Lin,Liaw. Metastatic Septic Endophthalmitis in Pyogenic Liver Abscess[J]. Journal of Clinical Gastroenterology，1988，10（5）：524-527.

[8] Liu, Cheng,Lin. Klebsiella Pneumoniae Liver Abscess Associated with Septic Endophthalmitis[J]. Archives of Internal Medicine，1986，146（10）：1913-1916.

[9] Lee, Lee.Park. Antimicrobial Resistance of Hypervirulent Klebsiella Pneumoniae: Epidemiology, Hypervirulence-Associated Determinants, and Resistance Mechanisms[J]. Frontiers in Cellular and Infection Microbiology, 2017, 74 (3): 89-92.

[10] Guo, Wang, Zhan, et al. Microbiological and Clinical Characteristics of Hypermucoviscous Klebsiella Pneumoniae Isolates Associated with Invasive Infections in China[J]. Frontiers in Cellular and Infection Microbiology, 2017, 724 (2): 192-197.

[11] Zhang, Zhao, Wang, et al. High Prevalence of Hypervirulent Klebsiella Pneumoniae Infection in China: Geographic Distribution, Clinical Characteristics, and Antimicrobial Resistance[J]. Antimicrobial Agents and Chemotherapy, 2016, 60 (4): 6115-6120.

[12] Ye, Tu, Jiang, et al. Clinical and Genomic Analysis of Liver Abscess-Causing Klebsiella Pneumoniae Identifies New Liver Abscess-Associated Virulence Genes[J]. Frontiers in Cellular and Infection Microbiology, 2016, 6 (5): 61-65.

[13] Bialek-Davenet, Nicolas-Chanoine, Decre, et al. Microbiological and Clinical Characteristics of Bacteraemia Caused by the Hypermucoviscosity Phenotype of Klebsiella Pneumoniae in Korea[J]. Epidemiology and Infection, 2013, 141 (1): 188-192.

[14] Cubero, Grau, Tubau, et al. Hypervirulent Klebsiella Pneumoniae Clones Causing Bacteraemia in Adults in a Teaching Hospital in Barcelona, Spain (2007-2013) [J]. Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 2016, 22 (2): 154-160.

[15] Peirano, Pitout, Laupland, et al. Population-based Surveillance for Hypermucoviscosity Klebsiella Pneumoniae Causing Community-acquired Bacteremia in Calgary, Alberta[J]. The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses et de la Microbiologie Medicale, 2013, 24 (3): e61-64.

[16] Tan, Cheng, Ong, et al. Performance Characteristics and Clinical Predictive Value of the String Test for Detection of Hepato-virulent Klebsiella Pneumoniae Isolated from Blood Cultures[J]. Diagnostic Microbiology and Infectious Disease, 2014, 78 (2): 127-128.

[17] Paczosa,Mecsas. Klebsiella Pneumoniae: Going on the Offense with a Strong Defense[J]. Microbiology and Molecular Biology Reviews : MMBR, 2016, 80 (3): 629-661.

[18] Yao, Xiao, Wang, et al. Clinical and Molecular Characteristics of Multi-clone Carbapenem-resistant Hypervirulent (hypermucoviscous) Klebsiella Pneumoniae Isolates in a Tertiary Hospital in Beijing, China[J]. International Journal of Infectious Diseases, 2015, 37 (1): 107-112.

[19] Luo, Wang, Ye, et al. Molecular Epidemiology and Virulence Factors of Pyogenic Liver Abscess Causing Klebsiella Pneumoniae in China[J]. Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 2014, 20 (11): 818-824.

[20] Shi, Lan, Huang, et al. Diversity of Virulence Level Phenotype of Hypervirulent Klebsiella Pneumoniae from Different Sequence Type Lineage[J]. BMC Microbiol, 2018, 18 (1): 94-95.

[21] Hsieh, Lin, Lee, et al. Serum-induced Iron-acquisition Systems and TonB Contribute to Virulence in Klebsiella Pneumoniae Causing Primary Pyogenic Liver Abscess[J]. The Journal of Infectious Diseases, 2008, 197 (12): 1717-1727.

[22] Jay Prakash Sah, Sanjay Kumar Shah, Bhupendra Sharma, et al. Siderophore Production: A Unique Quality of Pathogenic Klebsiella Pneumonia to Survive in Low Iron Concentration[J]. Asian Journal of Medical and Biological Research, 2015, 1 (1): 130-138.

[23] Russo, Shon, Beanan, et al. Hypervirulent K. Pneumoniae Secretes More and More Active Iron-acquisition Molecules than "Classical" K. pneumoniae Thereby Enhancing Its Virulence[J]. PLoS One, 2011, 6 (10): 26-34.

[24] Shah, Ni, Sun, et al. The Determination and Correlation of Various Virulence Genes, ESBL, Serum Bactericidal Effect and Biofilm Formation of Clinical Isolated Classical Klebsiella Pneumoniae and Hypervirulent Klebsiella pneumoniae from Respiratory Tract Infected Patients[J]. Polish Journal of Microbiology, 2017, 66 (4): 501-508.

[25] Shankar, Nabarro, Devanga Ragupathi, et al. Draft Genome Sequences of Three Hypervirulent Carbapenem-Resistant Klebsiella Pneumoniae Isolates from Bacteremia[J]. Genome announcements, 2016, 4(6): 121-123.

[26] Bialek-Davenet, Criscuolo, Ailloud, et al. Genomic Definition of Hypervirulent and Multidrug-resistant Klebsiella Pneumoniae Clonal Groups[J]. Emerging Infectious Diseases, 2014, 20(11): 1812-1820.

[27] Lin, Koh, Lee, et al. Genotypes and Virulence in Serotype K2 Klebsiella Pneumoniae from Liver Abscess and Non-infectious Carriers in Hong Kong, Singapore and Taiwan[J]. Gut pathogens, 2014, 621(2): 88-89.

[28] Navon-Venezia, Kondratyeva,Carattoli. Klebsiella Pneumoniae: a Major Worldwide Source and Shuttle for Antibiotic Resistance[J]. FEMS Microbiology Reviews, 2017, 41(3): 252-275.

[29] Hennequin,Robin. Correlation between Antimicrobial Resistance and Virulence in Klebsiella Pneumoniae[J]. European Journal of Clinical Microbiology & Infectious Diseases : Official Publication of the European Society of Clinical Microbiology, 2016, 35(3): 333-341.

[30] Chew, Lin,Teo. Klebsiella Pneumoniae in Singapore: Hypervirulent Infections and the Carbapenemase Threat[J]. Frontiers in Cellular and Infection Microbiology, 2017, 75(2): 13-15.

[31] Wu, Ma, Turton, et al. Virulence Genes in Isolates of Klebsiella Pneumoniae from the UK during 2016, Including among Carbapenemase Gene-positive Hypervirulent K1-ST23 and 'Non-hypervirulent' Types ST147, ST15 and ST383[J]. PloS one, 2018, 67(1): 118-128.

[32] Gu, Dong, Zheng, et al. A Fatal Outbreak of ST11 Carbapenem-resistant Hypervirulent Klebsiella Pneumoniae in a Chinese Hospital: a Molecular Epidemiological Study[J]. The Lancet Infectious Diseases, 2018, 18(1): 37-46.

[33] Zhang, Lin, Chan, et al. Emergence of Carbapenem-Resistant Serotype K1 Hypervirulent Klebsiella Pneumoniae Strains in China[J]. Antimicrobial Agents and Chemotherapy, 2016, 60(1): 709-711.

[34] Feng, Lu, Yao, et al. Carbapenem-Resistant Hypervirulent Klebsiella Pneumoniae of Sequence Type 36[J]. Antimicrobial Agents and Chemotherapy, 2018, 62(7): 35-41.

[35] Mohammad Ali Tabrizi, Badmasti, Shahcheraghi, et al. Outbreak of Hypervirulent Klebsiella Pneumoniae Harboring blaVIM-2 among Mechanically Ventilated drug Poisoning Patients with High Mortality Outcome in Iran[J]. J Glob Antimicrob Resist, 2018, 20(6): 20-25.

[36] Roulston, Bharucha, Turton, et al. A Case of NDM-Carbapenemase-producing Hypervirulent Klebsiella Pneumoniae Sequence Type 23 from the UK[J]. JMM Case Reports, 2018, 5(9): 34-38.

[37] Lee, Liu, Su, et al. Hypermucoviscosity Associated with Klebsiella Pneumoniae-mediated Invasive Syndrome: a Prospective Cross-sectional Study in Taiwan[J]. International Journal of Infectious Diseases, 2010, 14(8): e688-e692.

[38] Liu, Li, Zhang, et al. Clinical and Molecular Characteristics of Emerging Hypervirulent Klebsiella Pneumoniae Bloodstream Infections in Mainland China[J]. Antimicrobial Agents and Chemotherapy, 2014, 58(9): 5379-5385.

[39] Li, Sun, Yu, et al. Increasing Occurrence of Antimicrobial-Resistant Hypervirulent (hypermucoviscous) Klebsiella Pneumoniae Isolates in China[J]. Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 2014, 58(2): 225-232.

[40] Khaertynov, Anokhin, Davidyuk, et al. Case of Meningitis in a Neonate Caused by an Extended-Spectrum-Beta-Lactamase-Producing Strain of Hypervirulent Klebsiella Pneumoniae[J]. Frontiers in Microbiology, 2017, 81(5): 76-83.

[41] Yan, Zhou, Zou, et al. Hypervirulent Klebsiella Pneumoniae Induced Ventilator-associated Pneumonia in Mechanically Ventilated Patients in China[J]. European Journal of Clinical Microbiology & Infectious Diseases : Official Publication of the European Society of Clinical Microbiology, 2016, 35(3): 387-396.

[42] Surgers, Boyd, Girard, et al. ESBL-Producing Strain of Hypervirulent Klebsiella Pneumoniae K2, France[J]. Emerging Infectious Diseases, 2016, 22(9): 1687-1688.

[43] Shankar, Santhanam, Kumar, et al. Draft Genome Sequence of an Extended-Spectrum-beta-Lactamase-Positive

Hypervirulent Klebsiella Pneumoniae Strain with Novel Sequence Type 2318 Isolated from a Neonate[J]. Genome Announcements, 2016, 4(6): 88-91.

[44] Lee, Lee, Park, et al. Global Dissemination of Carbapenemase-Producing Klebsiella Pneumoniae: Epidemiology, Genetic Context, Treatment Options, and Detection Methods[J]. Frontiers in Microbiology, 2016, 7(9): 121-154.

[45] Oliva, Scorzolini, Castaldi, et al. Double-carbapenem Regimen, Alone or in Combination with Colistin, in the Treatment of Infections Caused by Carbapenem-resistant Klebsiella Pneumoniae (CR-Kp)[J]. Journal of Infection, 2017, 74(1): 103-106.

[46] Van Boeckel, Gandra, Ashok, et al. Global Antibiotic Consumption 2000 to 2010: an Analysis of National Pharmaceutical Sales Data[J]. The Lancet Infectious Diseases, 2014, 14(8): 742-750.

[47] Liu, Wang, Walsh, et al. Emergence of Plasmid-mediated Colistin Resistance Mechanism MCR-1 in Animals and Human Beings in China: A Microbiological and Molecular Biological Study[J]. The Lancet. Infectious Diseases, 2016, 16(2): 161-168.

[48] Gu, Huang, Ma, et al. Detection of Colistin Resistance Gene mcr-1 in Hypervirulent Klebsiella Pneumoniae and Escherichia coli Isolates from an Infant with Diarrhea in China[J]. Antimicrobial Agents and Chemotherapy, 2016, 60(8): 5099-5100.

[49] Choi, Ko. Loss of Hypermucoviscosity and Increased Fitness Cost in Colistin-resistant Klebsiella Pneumoniae Sequence Type 23 Strains[J]. Antimicrobial Agents and Chemotherapy, 2015, 59(11): 6763-6773.

[50] Andrade, Vitali, Gaspar, et al. Expansion and Evolution of a Virulent, Extensively Drug-resistant (polymyxin B-resistant), QnrS1-, CTX-M-2-, and KPC-2-producing Klebsiella Pneumoniae ST11 International High-risk Clone[J]. Journal of Clinical Microbiology, 2014, 52(7): 2530-2535.

[51] Magiorakos, Srinivasan, Carey, et al. Multidrug-resistant, Extensively Drug-resistant and Pandrug-resistant Bacteria: an International Expert Proposal for Interim Standard Definitions for Acquired Resistance[J]. Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 2012, 18(3): 268-281.

[52] Karaiskos,Giamarellou. Multidrug-resistant and Extensively Drug-resistant Gram-negative Pathogens: Current and Emerging Therapeutic Approaches[J]. Expert Opinion on Pharmacotherapy, 2014, 15(10): 1351-1370.

[53] Huang, Chou, Liang, et al. Emergence of an XDR and Carbapenemase-producing Hypervirulent Klebsiella Pneumoniae Strain in Taiwan[J]. The Journal of Antimicrobial Chemotherapy, 2018, 73(8): 2039-2046.

[54] Moura, Esposito, Fernandes, et al. Genome Sequence Analysis of a Hypermucoviscous/Hypervirulent and MDR CTX-M-15/K19/ST29 Klebsiella Pneumoniae Isolated from Human Infection[J]. Pathogens and Disease, 2017, 75(9): 89-93.

[55] Goncalves, Furlan, Vespero, et al. Spread of Multidrug-resistant High-risk Klebsiella Pneumoniae Clones in a Tertiary Hospital from Southern Brazil[J]. Infect Genet Evol, 2017, 13(9): 561-7.

（收稿日期 2018年12月10日 编辑 范玉明）