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Hans汉斯

碳青霉烯类耐药高毒力肺炎克雷伯菌的研究进展

上官小容

山东大学齐鲁医学院公共卫生学院职业与环境健康学系，山东 济南

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摘　要

高毒力和碳青霉烯类耐药已成为肺炎克雷伯菌(KP)的两个不同的进化方向，在临床环境中构成巨大威胁。然而，近年来发现越来越多的KP菌株整合了这两种表型，导致了毁灭性的临床结果。碳青霉烯耐药高毒力肺炎克雷伯菌(CR-hvKP)出现在2010年代初期，此后变得越来越普遍。CR-hvKP主要流行于亚洲，尤其是中国，但世界各地都有报道。CR-hvKP出现的机制可以总结为三种模式：1) 获得碳青霉烯类耐药表型的高毒力肺炎克雷伯菌(hvKP)；2) 耐碳青霉烯类肺炎克雷伯菌(CRKP)获得高毒力表型；3) 肺炎克雷伯菌获得碳青霉烯类耐药和高毒力的融合质粒。随着CR-hvKP的全球传播，应更加重视对CR-hvKP的持续监测。

关键词

肺炎克雷伯菌，高毒力，碳青霉烯类耐药

Research Progress of Carbapenem-Resistant Hypervirulent *Klebsiella pneumoniae*

Xiaorong Shangguan

Department of Occupational and Environmental Health, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan Shandong

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Abstract

High virulence and carbapenem resistance have become two different evolutionary directions of *Klebsiella pneumoniae* (KP), posing a great threat in clinical settings. However, in recent years, more

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and more KP strains have been found to integrate these two phenotypes, leading to devastating clinical outcomes. Carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (CR-hvKP) emerged in the early 2010s and has since become more common. CR-hvKP is mainly prevalent in Asia, especially China, but has been reported around the world. The mechanism of the emergence of CR-hvKP can be summarized into three patterns: 1) Hypervirulent *Klebsiella pneumoniae* (hvKP) which obtained carbapenem-resistant phenotype; 2) Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) obtained a hypervirulent phenotype; 3) *Klebsiella pneumoniae* obtained carbapenem-resistance and high virulence fusion plasmid. With the global spread of CR-hvKP, more attention should be paid to the continuous monitoring of CR-hvKP.

Keywords

***Klebsiella pneumoniae*, Hypervirulence, Carbapenem-Resistance**

1. 前言

肺炎克雷伯菌(KP)是医院最常见的条件致病细菌之一，近几十年在世界范围内越来越受到关注，这主要是由于其增强的耐药性和近期聚焦的高毒力[1] [2]。碳青霉烯类耐药肺炎克雷伯菌(CRKP)在 KP 菌株中的发生率已达到 30.0%以上[3]。CRKP 在世界范围内迅速传播，由于其高发病率和死亡率、治疗选择有限、住院时间长和治疗费用高，对人类健康和公共卫生构成严重威胁[4]-[8]。肺炎克雷伯菌通常分为经典肺炎克雷伯菌(cKP)和 hvKP 两种类型。hvKP 因其高毒性而备受关注，它能引发严重的感染，特别是化脓性肝脓肿[9]、眼内炎[10]和危及生命的脑膜炎[11]。然而，hvKP 和 CRKP 这两者的界限正在消失。近来分离出越来越多同时具有碳青霉烯耐药性和高毒力特征的 KP 菌株(CR-hvKP) [12]。CR-hvKP 的出现是毁灭性的，因为它同时具有多重耐药性、高毒力和高度传染性，将给临床治疗带来巨大的挑战[13]。本综述的目的是总结当前对 CR-hvKP 的相关研究，深入阐述其流行病学特征、形成机制及治疗和预防措施，为其防控提供科学依据。

2. CR-hvKP 的流行病学特征

CR-hvKP 最早在 2012 年中国检出[14]，随后逐渐被临床所关注，陆续在其他国家都有检出，例如美国[15] [16]、印度[17]、俄罗斯[18]、埃及[19]、意大利[20]、法国[21]、德国[22]、伊朗[23]、新加坡[24]、澳大利亚[25]等许多国家。因此，CR-hvKP 的感染非常严峻，已在全球蔓延。

CR-hvKP 的发病率在全球范围内一直在增加[26]。大多数 CR-hvKP 病例在亚洲临床环境中报道，特别是中国已被确定为 CR-hvKP 的主要流行地区，其报告病例数最多[27]。CR-hvKP 的发病率在中国大陆一半以上的地区一直在增加，并且存在显著的地区差异。发病率最高的是浙江、江苏和北京，其次是河南、山东和河北[12]。根据中国 CR-hvKP 的流行病学分析，ST11 是中国最常见的 CRKP 克隆，并且 80%的 CR-hvKP 菌株属于 ST11 和产 KPC-2 型[28]。2016 年以来，中国 ST11 CRKP 的优势克隆由于重组从 KL47 转移到 KL64 [13]。ST11-KL64 菌株对恶劣条件的抵抗力更强，毒力也更高，并且在 ST11-KL64 克隆中更频繁地发现 pLVPK 样毒力质粒[13]。欧洲和美洲的 CR-hvKP 发病率第二高，主要以 ST23 和 K1/K2 荚膜血清型菌株为代表。欧洲的主要碳青霉烯类耐药基因是 bla_{NDM} 和 bla_{OXA} [22] [29] [30]，而 bla_{KPC-2} 在

美洲更为普遍[31] [32]。

3. CR-hvKP 的形成机制

复杂多样的进化机制可提高 KP 菌株的毒力和抗生素耐药性，是增加相关传染病发病率和死亡率的关键因素。这就是低毒力 cKP 和 CRKP 菌株或抗生素耐药性低的菌株进化为具有更强毒力、高碳青霉烯类耐药性和全球传播特征的“超级细菌”CR-hvKP 的主要原因。据文献报道，CR-hvKP 的形成可主要分为三种模式，具体如下。

3.1. hvKP 菌株获得碳青霉烯类耐药质粒

CRKP 中携带可移动碳青霉烯类抗性基因的质粒、转座子、噬菌体和插入元件可以水平转移到 hvKP 菌株上，形成 CR-hvKP 菌株[26]。根据不同的地理区域，获得性碳青霉烯类耐药表型与流行耐药机制相关。例如，bla_{KPC} 是中国和美国最常见的碳青霉烯酶基因[33]，bla_{KPC} 阳性的 CR-hvKP 菌株在这些地区的报道也更频繁。2014 年，美国的一项研究首次报道了一种高粘液粘性 ST23 KP 菌株，该菌株获得了 bla_{KPC-2} 并进化成多重耐药性 CR-hvKP [15]。同样，中国报道了 5 种 K1 hvKP 菌株，它们通过获得含有 bla_{KPC-2} 基因的毒力质粒或组合携带 bla_{KPC-2} 的可移动 DNA 片段形成 K1 CR-hvKP [34]。此外，NDM 和 OXA 在俄罗斯和印度更为常见。2018 年，俄罗斯研究人员首次报道 ST23 和 K1 hvKP 获得同时携带 $bla_{CTX-M-15}$ 和 bla_{OXA-48} 的质粒，并进化成 CR-hvKP [29]。印度还报道了一种携带 bla_{OXA} 和 bla_{NDM} 基因的 hvKP 菌株导致两人死亡[17]。

值得注意的是，与多重耐药(MDR)基因组相比，高毒力谱系的复制子标志物明显较少，尤其是 CG23 谱系；同时高毒力克隆的质粒多样性也低于 MDR 克隆[25]。这些证据可能表明，高毒力克隆不太容易获得额外的质粒，或者在维持已经获得的质粒方面存在缺陷。

3.2. CRKP 菌株获得毒力质粒

毒力质粒的获得是 CRKP 菌株毒力增加的关键机制，这是三种机制中最普遍的。最著名的毒力质粒是来自肺炎克雷伯菌 NTUH-K2044 的质粒 pK2044 (224 kb)和来自肺炎克雷伯菌 CG43 的质粒 pLVPK (219 kb) [35]。这种毒力质粒是非偶联性的，并且由于缺乏包含 tra 基因的完整偶联模块，因此在 cKP 菌株中不存在[36]。然而，近年来 CRKP 菌株获得 pLVPK 样毒力质粒的报道频发，并且以这种方式形成的产 KPC 碳青霉烯酶的 ST11 CR-hvKP 菌株在中国占绝对优势。有相关研究表明，在特定条件下，hvKP 菌株的非共轭毒力质粒可以被属于不相容组 F (IncF)的共轭质粒动员到 ST11 CRKP 菌株中[37]。在此之后，属于不同不相容基团的几个共轭辅助质粒(包括 IncN3，IncB/O/K/Z 和 Incl1)可以动员共存的非共轭毒力质粒[38]-[40]。与共轭质粒相反，毒力质粒可以逃避成簇的规则间隔短回文重复序列(CRISPR)/CRISPR 相关蛋白(Cas)系统防御机制，并在受体菌株中稳定存在[41]。这些研究强调了可动员质粒作为肺炎克雷伯菌毒力基因传播的关键载体的威胁。此外，将 hv 质粒的片段整合到偶联的 IncFIB/IncFIA 质粒中可产生偶联毒力质粒[42] [43]。鉴于有证据表明 CRKP 菌株可以以较低的适应成本维持多个质粒[44] [45]，并且这些质粒的获得或丢失经常发生在医院环境中的肺炎克雷伯菌株之间[46]。这个过程可能有助于毒力编码元件在 CRKP 菌株之间快速传播，并且很容易传播并导致爆发。

3.3. KP 获得携带毒力和碳青霉烯类耐药基因的融合质粒

近年来，许多研究报道了 CR 和毒力相结合的融合质粒。融合质粒的形成可能是由不同质粒之间的各种相互作用引起的，包括毒力和 CR 质粒骨架的重组、毒力决定簇插入 CR 质粒或将 CR 决定簇插入毒

力质粒[47]。在 KP 菌株中已有不同序列类型的杂交质粒报道，包括典型的 cKP (ST11、ST15 和 ST147)和 hvKP 类型(ST23 和 ST86) [30] [48]-[51]。关于融合质粒形成的机制，有研究表明两个单链片段可以在特定位点进行同源重组或进行独特的融合，最终导致融合质粒的产生[37]。这一结果阐明了融合质粒发育的基础过程，并强调了质粒的动态性质及其交换遗传信息的能力，这可能导致具有不同遗传性状的融合质粒的出现。这些趋同菌株和质粒的适应性和传播性仍不清楚，未来需要更加深入的研究。

4. CR-hvKP 治疗和预防措施

高水平的耐药性和致病性通常会导致不良的临床结局[52] [53]。到目前为止，尚无针对 CR-hvKP 的确定性治疗方法，大多参照碳青霉烯耐药肠杆菌科细菌(CRE)的治疗指南。头孢他啶/阿维巴坦(CZA)是一种新型的 β-内酰胺/β-内酰胺酶抑制剂组合，治疗 CRKP 引起的中枢神经系统感染时，以 CZA 为基础的联合治疗更成功[54]。然而，在临床使用过程中，极易诱导 bla_{KPC-2} 或 bla_{KPC-3} 突变并获得对 CZA 的耐药[55] [56]。多粘菌素 E 和多粘菌素 B(PMB)是两种临床可用的多粘菌素，它被认为是由 MDR 革兰氏阴性菌引起的感染的最后一线治疗选择[57]，但真正的疗效却不尽如人意[58]。但联合治疗可增强抗菌活性，例如 PMB 与米诺环素或利福平的组合对 NDM-1 和 OXA-48 样 KP 有效[59]；PMB 与磷霉素联合使用具有免疫调节作用和显着的细菌杀灭作用[60]。另外，经验性使用替加环素是 ST11-KL64 CRKP 感染患者死亡的独立危险因素[61]，并导致 CR-hvKP 菌株的广泛传播[62]。

此外，噬菌体疗法可以治疗由高毒力和耐碳青霉烯类肺炎克雷伯菌引起的呼吸道、胃肠道、皮肤软骨组织和尿路感染，以及非酒精性脂肪肝和菌血症[63]-[65]。预适应噬菌体疗法与抗生素联合治疗有望治疗 CR-hvKP，因为它们可以减少抗生素的剂量并抑制耐药细菌的出现[66] [67]。

CR-hvKP 的预防要从控制传染源，切断传播途径和保护易感人群三方面展开。首先，对于 CR-hvKP 感染患者，应当及时发现并隔离治疗。针对性且合理化的抗生素治疗十分关键，早日使患者恢复。其次是切断 CR-hvKP 的传播途径。高危患者应在入院时接受筛查，并在住院期间定期进行 CRKP/hvKP 的监测。另外，医务工作者的手部消毒也是必不可少的。最后保护易感人群是预防 CR-hvKP 感染的重要环节。开发针对 CR-hvKP 菌株的疫苗将建立起人群屏障。此外，提高个体免疫力也至关重要，提倡健康饮食、体育锻炼和规律作息等。

5. 小结

总之，CR-hvKP 出现在 2010 年代初期，此后变得越来越普遍。CR-hvKP 主要流行于亚洲，尤其是中国，并在世界各地都有报道。CR-hvKP 出现的机制可归纳为三种模式：(1) hvKP 获得碳青霉烯类耐药表型；(2) CRKP 获得高毒力表型；(3) 肺炎克雷伯菌获得碳青霉烯类耐药和高毒力的融合质粒。随着 CR-hvKP 的全球传播，应更加重视对 CR-hvKP 出现的持续监测。

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