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碳青霉烯耐药肺炎克雷伯菌头孢他啶－阿维巴坦耐药机制研究进展综述

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摘　要

头孢他啶－阿维巴坦被称为碳青霉烯耐药肺炎克雷伯菌(Carbapenem-Resistant *Klebsiella pneumoniae*, CRKP)的最后一道防线，随着临床上的不合理使用，越来越多的耐药机制被报道，最常见的有*β*-内酰胺酶关键位点氨基酸突变、*bla*$_{KPC}$基因过表达及膜孔蛋白突变导致细胞膜通透性障碍。本文详细地总结了头孢他啶－阿维巴坦的药理特点、耐药现状，以及耐药机制，旨在给头孢他啶－阿维巴坦耐药防控及多重耐药肺炎克雷伯杆菌的临床治疗提供科学思路。

关键词

碳青霉烯耐药肺炎克雷伯菌，头孢他啶－阿维巴坦耐药，KPC突变

A Review of Research Progress on the Mechanisms of Resistance to Ceftazidime-Avibactam in Carbapenem-Resistant *Klebsiella pneumoniae*

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Abstract

Ceftazidime-avibactam is regarded as the last line of defense against Carbapenem-resistant *Klebsiella pneumoniae* (CRKP). However, with its irrational clinical use, an increasing number of resistance mechanisms have been reported. The most common mechanisms include amino acid mutations at critical sites of *β*-lactamases, overexpression of the *bla*$_{KPC}$ gene, and mutations in porin proteins that lead to impaired cell membrane permeability. This article provides a detailed summary of the pharmacological characteristics, current resistance status, and resistance mechanisms of ceftazidime-avibactam, aiming to offer scientific insights for the prevention and control of ceftazidime-avibactam resistance and the clinical treatment of multidrug-resistant *Klebsiella pneumoniae*.

Keywords

Carbapenem-Resistant *Klebsiella pneumoniae*, Ceftazidime-Avibactam Resistance, KPC Mutations

1. 引言

随着抗菌药物的使用，碳青霉烯耐药肺炎克雷伯菌(Carbapenem-Resistant *Klebsiella pneumoniae*, CRKP)作为医院感染的主要病原体之一，它的高耐药性、高传播性、高病死率已对临床的抗感染治疗构成了严峻挑战[1]。2024 年，WHO 发布的最新细菌优先病原体预警清单中 CRKP 因为具有转移耐药基因的能力并可以引起严重的感染疾病被分为关键优先级组，被认为是造成重大全球负担的病原体之一[2]。头孢他啶－阿维巴坦(Ceftazidime-Avibactam, CZA)作为新型酶抑制剂合剂，在 CRKP 及其他多重耐药菌的重症感染中疗效显著。但是由于抗生素的不规范使用，越来越多的头孢他啶/阿维巴坦耐药菌株被报道。故本综述从 CRKP 的 CZA 耐药性变迁及可能的机制分析，深度解析 CZA 耐药 CRKP 的研究进展，旨在给头孢他啶/阿维巴坦耐药防控及多重耐药肺炎克雷伯杆菌的临床治疗提供科学思路。

2. 头孢他啶－阿维巴坦的药理特点

头孢他啶－阿维巴坦是头孢他啶和阿维巴坦(Avibactam, AVI)组成的新型酶抑制剂合剂，在 2019 年 5 月 21 日获得国家药品监督管理局(CFDA)批准在我国上市，适用于复杂性腹腔感染、医院获得性肺炎和呼吸机相关性肺炎[3]。其中头孢他啶是第三代头孢菌素，通过与细菌细胞中的青霉素结合蛋白相结合，使转肽酶酰化，抑制细菌的细胞壁合成，影响细胞壁粘肽成分的交叉连结，使细菌分裂和生长受到抑制从而杀灭细菌。阿维巴坦则属于二氮杂双环辛酮化合物，是一种新型 *β*-内酰胺酶抑制剂，它通过酰胺键与亲核进攻的 *β*-内酰胺酶丝氨酸开环形成共价结合物，得到稳定的酶抑制剂复合体，且不发生水解，再经环合形成内酰胺环和阿维巴坦。在此过程中，亲核进攻导致开环的速率远远大于环合，致使 *β*-内酰胺酶基本处于抑制状态，而阿维巴坦则可以通过缓慢的可逆共价反应恢复活性，因此具有长效的抑酶作用，能有效阻止头孢他啶被 *β*-内酰胺酶水解失活，保护头孢他啶对产 *β*-内酰胺酶肠杆菌的抗菌活性，这也是它和其他传统的 *β*-内酰胺酶抑制剂相比最大的优势。

它除了对 Ambler 分类中的 B 类金属酶(如新德里金属 *β*-内酰胺酶，New Delhi Metallo-*β*-Lactamase,

NDM)没有抑制能力[4]-[6]，对 A 类酶(如肺炎克雷伯菌碳青霉烯酶，*Klebsiella pneumoniae* Carbapenemase, KPC)、C 类酶(如头孢菌素酶，AmpC)和某些 D 类酶(如苯唑西林酶、Oxacillinase、OXA、OXA-48)都有广泛的抑制活性。中国细菌耐药监测网数据显示，去年收集的 CRKP 二代测序分析结果中，CRKP 的碳青霉烯酶分布特征主要以产 KPC 酶为主，为 85.8%，其次为金属酶(11.1%)、OXA-48 酶(0.3%)以及双碳青霉烯酶(2.8%) (http://www.chinets.com/)。此外，相关报道显示儿童患者分离的碳青霉烯酶主要以 KPC、NDM 和 OXA-48 酶为主，而成人患者分离的主要以 KPC 酶为主[7] [8]。因此，头孢他啶－阿维巴坦已成为 CRKP 感染治疗的较优选择，尤其是在产 KPC 酶的肺炎克雷伯菌(KPC-producing *Klebsiella pneumoniae*, KPC-KP)中[9]-[11]。

3. 碳青霉烯耐药肺炎克雷伯菌头孢他啶－阿维巴坦的耐药现状

随着一线药物碳青霉烯类抗生素的临床使用，CRKP 的检出率日益增高。

国际最佳耐药性监测网络(International Network for Optimal Resistance Monitoring, INFORM)报道的数据显示，2012~2014 年美国医疗中心收集的 34,062 株肠杆菌中头孢他啶－阿维巴坦耐药率仅为 1.5%，其中 CRE 对头孢他啶－阿维巴坦的耐药率为 16.5%。在这 961 株 CRE 中共有 609 株携带一个或多个碳青霉烯酶并且没有携带产金属 *β*-内酰胺酶(Metallo-*β*-Lactamase, MBL)菌株，它们对头孢他啶－阿维巴坦的耐药率为 1.3% [12]。2015~2017 年间欧洲收集的 CRE 菌株的相关报道中，头孢他啶－阿维巴坦耐药株的检出率分别为 27%及 21.5%，MBL 阴性的菌株仍对其保持较高的敏感性(97.2%) [13] [14]。根据 ATLAS 结果显示，2017~2019 年间拉丁美洲收集的 CRE 中，头孢他啶－阿维巴坦耐药株的检出率为 25.3%。其中，MBL 阴性的 CRE 菌株对其耐药率为 0.6%，碳青霉烯酶阴性的 CRE 对其耐药率为 4.2% [15]。据亚太地区报道，肠杆菌对头孢他啶－阿维巴坦的耐药率为 0.4%及 1.9% [16] [17]，而 CRE 中 MBL 阴性的菌株耐药率为 12.3% [18]。而根据中国的细菌耐药监测网数据显示，我国肺炎克雷伯菌对美罗培南的耐药率从 2005 年的 2.9%已经增长到了 2024 年的 22.1%，在近 8 年间检出率持续维持在 20%以上高位，对头孢他啶－阿维巴坦的耐药率也高达 7.8%。其中 14,781 株 CRKP 中头孢他啶－阿维巴坦的耐药株检出率为 15.8%，这些菌株中产 KPC 型碳青霉烯酶肺炎克雷伯菌对头孢他啶－阿维巴坦的耐药率为 1.3% [19]。由此可见，世界范围内 CRE 对于头孢他啶－阿维巴坦的耐药率呈现一个缓慢上升的趋势，欧洲及拉丁美洲耐药率则稍偏高。其中大部分 CZA 耐药的 CRE 中，*bla*NDM 基因仍为最主要的碳青霉烯酶，而 MBL 阴性的 CRE 菌株耐药率仍较低。虽然头孢他啶－阿维巴坦仍是产 KPC 型 CRKP 的首选治疗药物，但是目前为止，由于药物的使用、细菌的进化及突变，越来越多的耐药机制被报道，尤其是 bla_{KPC} 酶变体的产生，目前已有超过 150 种酶变体被报道，它们的出现正在向全球公共卫生发起严峻的挑战[20]-[26]。

4. 耐药机制

CRKP 对头孢他啶/阿维巴坦耐药最常见的机制主要有以下几种，最常见的是产生 B 类金属酶。金属酶其活性依赖于酶中心的金属离子，如锌离子(Zn^{2+})，它共分为 3 大类，其中 B1 类是目前临床最多见的 MBL，例如 NDM (新德里金属内酰胺酶)、IMP (亚胺培南酶)和 VIM (维罗纳整合子编码的金属酶)。目前临床上常用的 *β*-内酰胺酶抑制剂(如克拉维酸、他唑巴坦、阿维巴坦等)均无法针对此金属活性中心发挥抑制作用，因此当细菌产生 MBL 时，头孢菌素仍会被直接水解而导致治疗失效[27]。此外，其他耐药机制主要有：*β*-内酰胺酶关键位点氨基酸突变；bla_{KPC} 基因过表达及膜孔蛋白突变导致细胞膜通透性障碍；以及较少见的外排泵过表达；青霉素结合蛋白等。本综述将详细介绍以下 2 点。

4.1. *β*-内酰胺酶关键位点氨基酸突变介导耐药

A 类 *β*-内酰胺酶关键位点氨基酸突变是导致头孢他啶－阿维巴坦耐药的另一大重要原因，包括 KPC

和 ESBL。作为肺炎克雷伯菌中最常见的碳青霉烯酶，KPC 几乎可以水解全部的 β-内酰胺类抗生素[28]。而 KPC 酶变体的出现是细菌在治疗过程中对头孢他啶－阿维巴坦产生耐药的最普遍原因。Ω 环则是构成 β-内酰胺酶活性中心的重要结构，它是位于 Arg164 和 Asp179 之间的盐桥，在结构的维持以及底物的识别催化中发挥了关键作用。如果它的氨基酸出现替换、缺失、重复等突变，将会导致环中氢键位置和结构的改变，最终从结合能力、催化活性、稳定性等多方面影响 β-内酰胺酶的功能[29] [30]。盐桥不但限制了整个环的灵活性，而且由于处于酶活性中心的结构、编码序列的单碱基易突变、富含 AT 碱基高突变热点的邻近，且突变后能有效增强耐药性等原因，在抗生素压力选择下更易成为“优势突变位点”[31]-[33]。

在 2017 年的一项回顾性研究中，Shields 等人首次发现了 3 例在治疗 CRE 感染过程中出现的 KPC-3 的 KPC-31 (D179/T243M)、KPC-32 (D179Y)和 KPC-8 (V240G)突变体，它们使头孢他啶－阿维巴坦的 MIC 值分别增加了 128 倍、16 倍和 4 倍[34]。随后他们又在一名肺炎克雷伯菌引起的菌血症患者的脓液中发现了 KPC-3 的另一种突变体(A177E、D179Y)，其在对头孢他啶阿维巴坦耐药后恢复了对美罗培南的敏感性[35]。我国在 2019 年头孢他啶－阿维巴坦获批临床使用后，KPC 突变体在革兰氏阴性杆菌中也呈现急剧增长的趋势，其中肺炎克雷伯菌的占比更是高达 73.8% [20]。

越来越多的头孢他啶阿维巴坦耐药的 KPC 突变体被报道，常见的有 KPC-2 的 D179Y 突变体 KPC-33，它可以扩大底物结合腔从而增强对头孢他啶的亲和力，同时使得阿维巴坦对它的抑制能力下降，最后通过水解 β-内酰胺类抗生素的 β-内酰胺环，使其失去抗菌活性。与此同时，在突变为 KPC-33 后，它丧失了水解碳青霉烯类药物的能力。但是现仍有较多临床菌株存在同时携带多个 KPC 酶的情况，从而同时导致头孢他啶－阿维巴坦以及碳青霉烯类药物 MIC 值的升高[23]。

另外，还有 KPC-2 来源的 D242-GT-243deletion、L169P、D163E、D179N、Y241H、H274N、D179Y、valine insertion after 262 position、Ser182dup、G239_V240del、del166Leu/167Asn and 242Gly/243Thr 的突变[36]-[42]，还有 KPC-3 来源的 V240A、D179Y、A172T、269-Pro-Asn-Lys-270、Arg-163-Ser、276-Glu-Ala-Val-277、LN169-170H、D179Y、A172T、del168Leu/169Asn and Ser170Pro、179ins Ser 的突变[43]-[50]。

产 ESBL 的革兰氏阴性菌是对广谱 β-内酰胺类抗生素耐药的主要原因，其中 CTX-M 酶为最常见的 ESBL [51]。目前 CTX-M-15 在世界范围内占主导地位，其次是 CTX-M-14 及 CTX-M-27，然而随着头孢他啶/阿维巴坦的使用，CTX-M 酶突变导致的耐药率呈现上升趋势。Both 等人曾在多重耐药的肺炎克雷伯菌分离株中发现 CTX-M-14Δ170Δ264 的突变体，它在出现两个氨基酸变化后导致头孢他啶和头孢他啶/阿维巴坦的 MIC 值升高了>64 和 16 倍，原因可能是突变体增强对头孢他啶的水解活性[52]。Livermore 等人的报道称[53]，在使用 2 × MIC 头孢他啶 + 1 mg/L 的药敏平板筛选产 ESBL 和 AmpC 的大肠杆菌时发现了一株 CTX-M-15 突变株，它在出现 Asp182Tyr 后，使头孢他啶/阿维巴坦的 MIC 值上升了 8 倍。在一些头孢他啶/阿维巴坦耐药的菌株中还发现了，CTX-M 突变体的克隆株虽然仍对头孢他啶/阿维巴坦敏感，但是却使 MIC 值升高 8 倍，并且可以联合 Ompk36 膜孔突变使得细菌产生耐药[54]。

除 A 类 β-内酰胺酶外，还有较少见的 D 类 β-内酰胺酶，比如 OXA-48 关键位点氨基酸突变同样可以导致头孢他啶－阿维巴坦耐药。有报道称在大肠杆菌中碳青霉烯酶 OXA-48 在头孢他啶－阿维巴坦治疗后出现了双氨基酸的替换(P68A 和 Y211S)，这导致了阿维巴坦的抑制能力降低为原来的 1/5。其中 P68A 替换增加了底物结合位点的灵活性和可塑性，Y211S 突变则影响了酶的稳定性，二者通过改变氢键提高了细菌对头孢他啶的耐药性[55]。另外，也有携带 OXA-40、66、69、88、93、94、95、96、206 酶的鲍曼不动杆菌对头孢他啶－阿维巴坦耐药[56]。截至目前，尚未分离出因 OXA 酶而产生头孢他啶－阿维巴坦耐药性的肺炎克雷伯菌菌株。

4.2. bla_{KPC} 基因过表达及孔蛋白突变介导耐药

早在 2015 年曾报道过，OmpK 膜孔蛋白的突变可能是导致 KPC-KP 菌株头孢他啶/阿维巴坦耐药的原因[57] [58]。第 1 例头孢他啶/阿维巴坦耐药的菌株被研究，发现它的 bla_{KPC-3} 的表达量是同源敏感株的 3.8 ± 0.2 倍，并且它存在 OmpK36 (T333N)的突变及合并有 OmpK35 的截断。当它回补正常的 OmpK35 和 OmpK36 后，头孢他啶/阿维巴坦的 MIC 均出现了明显下降[59]。Castanheira 等人在 2020 年从欧洲、拉丁美洲和亚太地区收集到的 286 株 CRE (其中 243 株为肺炎克雷伯菌)中研究发现，头孢他啶/阿维巴坦 MIC 值为 4 mg/L 的菌株均存在 OmpK35 缺失以及 OmpK36 的 L3 存在突变，并认为同时存在 bla_{KPC} 或 β-内酰胺酶产生突变将引起头孢他啶/阿维巴坦的 MIC 值升高[60]。随后越来越多的报道也证实了这一点，例如一株 ST258 的头孢他啶/阿维巴坦耐药的肺炎克雷伯菌被报道，它携带了 bla_{KPC-23}，并存在 OmpK35 缺失和 OmpK36 突变[43] [61] [62]。我国也有报道在 24 株仅携带 bla_{KPC} 的临床分离的肺炎克雷伯菌中发现，bla_{KPC} 在 MIC 值为 4 mg/mL~8 mg/mL 的菌株中，拷贝数和表达量要比 MIC ≤ 2 mg/mL 的菌株高 4.2~4.8 倍。并且在 MIC ≥ 1 mg/mL 的菌株中发现发生了 OmpK35 基因突变，并与 MIC ≤ 0.5mg/mL 的菌株相比，OmpK35 的 mRNA 表达水平下降了 28.5 倍，然而在回补正常的 OmpK35 孔蛋白后，它们对头孢他啶和头孢他啶/阿维巴坦的 MIC 下降了 2~4 倍[63]。

也有报道称在头孢他啶/阿维巴坦治疗后出现 4 株耐药菌株发生了 KPC 酶的突变，同时它们的 bla_{KPC} 基因表达量和拷贝数出现了增加，可能是导致 MIC 值最高升高了 1024 倍的原因。然而，这些耐药菌株和同源的敏感株菌存在 OmpK35 缺失和 OmpK36 突变，并且当进行野生型 OmpK35、OmpK36 的回补后，MIC 值并没有出现下降[64]。

5. 结论与展望

头孢他啶/阿维巴坦主要用于治疗由肺炎克雷伯菌、阴沟肠杆菌、大肠埃希菌、奇异变形杆菌和铜绿假单胞菌等革兰氏阴性杆菌引起的复杂腹腔内感染、医院获得性肺炎和呼吸机相关肺炎。尤其可用于治疗方案选择有限的 CRE、CRPA 等耐药菌株引起的感染。作为碳青霉烯耐药菌株的最后一道防线，头孢他啶/阿维巴坦在很大程度上缓解了多重耐药的革兰氏阴性杆菌治疗手段匮乏的现状。但是自 CZA-AVI 开始应用于临床，全球范围内已陆续有耐药菌株产生的报道，因此需迫切了解关于菌株产生头孢他啶/阿维巴坦耐药性的机制。其中在头孢他啶－阿维巴坦使用过程中出现 β-内酰胺酶关键位点的氨基酸突变屡见不鲜，还有 bla_{KPC} 基因过表达及膜孔蛋白突变、外排泵过表达、青霉素结合蛋白等均可介导耐药性的发生。

现阶段，针对产金属 β-内酰胺酶的 CAZ-AVI 天然耐药菌株已有广谱 β-内酰胺酶抑制剂，而针对 CAZ-AVI 非天然耐药菌株，由于多黏菌素、替加环素在疗效和安全性方面存在一些使用限制，新型 β-内酰胺酶抑制剂例如美罗培南－瓦博巴坦、亚胺培南－瑞莱巴坦在国内并未普及，目前临床上多提倡使用抗菌药物联合治疗。故此针对这类患者，需要我们临床工作者和检验科密切合作，加强沟通才能指导这类病人的精准用药。并且我们需要注意，现有越来越多 KPC 突变体的出现打破了碳青霉烯酶检测的传统实验室思维，使得检测结果出现碳青霉烯酶假阴性从而导致临床医生的误判。故此我们还提倡，对于重症患者，除了碳青霉烯酶的检测，还需同时完善 CAZ-AVI 药敏试验，尽早开始针对 KPC 突变体的精准治疗。总之，对于头孢他啶－阿维巴坦不断出现的复杂耐药机制，我们不但需要注意在临床工作中合理使用 CZA-AVI 以尽量减少细菌耐药性的出现，而且需要持续跟踪细菌耐药性发展的情况并指导开发新的治疗方法。

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