

细菌对碳青霉烯类抗生素的耐药机制与防治策略研究进展

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摘 要: 碳青霉烯类抗生素是治疗多重耐药革兰氏阴性菌感染的关键药物, 其耐药性的全球蔓延已成为临床抗感染领域面临的严峻问题。碳青霉烯耐药菌(CRO)的核心耐药机制包括: 碳青霉烯酶水解、外膜孔蛋白缺失、外排泵过表达、生物膜形成以及细菌靶位改变, 这些机制间存在显著的协同增效效应。耐药基因通过质粒、转座子进行水平转移, 并凭借环境-临床传播链持续扩散, 加剧了流行趋势。同时, 本文也系统阐述了CRO的防治策略, 包括新型 β -内酰胺酶抑制剂、外排泵抑制剂靶向干预、噬菌体-CRISPR基因编辑技术及多药联用方案。未来需深度融合耐药进化机制研究与跨学科干预, 为遏制碳青霉烯耐药提供解决方案。

关键词: 碳青霉烯类抗生素; 细菌耐药; 耐药机制; 基因水平转移; 防控策略

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Research progress on the resistance mechanism of bacteria to carbapenem antibiotics and control strategies

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Abstract: Carbapenem antibiotics are key drugs for treating life-threatening infections caused by multidrug-resistant Gram-negative bacteria, because of their broad antibacterial spectrum and stability against most β -lactamases. However, the increasingly serious carbapenem-resistant organisms (CROs) infections have become a major challenge in the field of anti-infection. This review summarizes the resistance mechanism of CRO, the dissemination of CRO, as well as the prevention and control strategies and current situation of CRO. The development of CRO resistance often results from the synergistic effects of multiple mechanisms. Key resistance mechanisms include: (1) production of carbapenemases that hydrolyze carbapenems, including serine β -lactamases (Ambler classes A and D, e.g., KPC, OXA-48) and metallo- β -lactamases (class B, e.g., NDM, VIM, IMP); (2) reduced drug permeability due to mutations or loss of outer membrane porins (e.g., OmpK35/OmpK36 in *Enterobacteriaceae*, OprD in *P. aeruginosa*), limiting antibiotic influx; (3) overexpression of multidrug efflux pumps (e.g., AcrAB-TolC, MexAB-OprM, AdeABC), which actively expel antibiotics; (4) enhanced biofilm formation, creating a physiological barrier that restricts antibiotic penetration and promotes a tolerant, slow-growing population; and (5) mutations or modifications at the target site, particularly mutations or modifications in penicillin-binding proteins (PBPs). These mechanisms rarely function independently but often work together, thereby enhancing drug resistance. For example, porin loss combined with weak hydrolysis by extended-spectrum β -lactamases (ESBLs) or AmpC enzymes can confer significant resistance to carbapenems such as ertapenem. The rapid dissemination of carbapenem resistance is propelled by two main drivers: efficient horizontal gene transfer (HGT) and the global spread of successful clones. Key resistance genes, notably *bla*_{KPC}, *bla*_{NDM}, and *bla*_{OXA-48-like}, are frequently located on mobile genetic elements such as conjugative plasmids, transposons, and integrative and conjugative elements (ICEs), facilitating rapid dissemination across bacterial species and genera. Common environmental stressors in healthcare and community settings, including subinhibitory concentrations of

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antibiotics, disinfectants (such as chlorinated compounds), and heavy metals, can further promote HGT by triggering bacterial stress responses such as the SOS response. Clonal lineages characterized by strong environmental fitness/persistence, and high pathogenicity have become predominant on a global scale, such as *Klebsiella pneumoniae* sequence type (ST) 11 (and its sublineage ST11-KL64) in Asia, *Acinetobacter baumannii* international clone (IC) 2, and *Pseudomonas aeruginosa* ST235. These clones disseminate widely through healthcare networks, international travel, and environmental reservoirs, forming a persistent and mobile drug-resistant pool. Active screening is one of the core strategies for containing the intra-hospital transmission of CRO-resistant bacteria. Rapid molecular testing (e.g., PCR for carbapenemase genes), combined with stringent infection control measures (contact isolation, enhanced environmental cleaning), remains fundamental for containment of CRO. Currently, clinical treatment for CRO infections primarily relies on multidrug combination therapy, with the specific regimen determined by the pathogen's drug resistance phenotype and the site of infection. The new treatment strategies currently under development include: (1) developing novel inhibitors targeting specific resistance mechanisms, such as MBL inhibitors and efflux pump blockers; (2) exploring "drug repurposing" strategies to identify β -lactamase inhibitory activity in existing non-antibiotic drugs (e.g., the antifungal agent tavaborole); (3) applying precision biocontrol agents like engineered bacteriophages and CRISPR-Cas systems to selectively lyse resistant bacteria or inactivate resistant genes; and (4) optimizing synergistic combination regimens, such as fosfomycin paired with a carbapenem or a novel β -lactamase inhibitor. In summary, the CRO crisis demands integrated strategies: developing resistance-breaking agents (e.g., dual-function molecules or combination strategies) to counter synergistic resistance mechanisms and implementing proactive One Health surveillance to track high-risk clones across clinical and environmental settings.

Key words: carbapenem antibiotics; bacterial resistance; resistance mechanism; horizontal gene transfer; prevention and control strategy

碳青霉烯类抗生素是治疗多重耐药革兰阴性菌感染的关键药物,但碳青霉烯耐药菌(carbapenem-resistant organism, CRO)的全球暴发已构成严峻公共卫生危机。既往研究聚焦单一耐药机制:碳青霉烯酶水解、孔蛋白缺失、外排泵过表达、生物膜产生及细菌靶位改变,而对“酶-孔蛋白-外排泵-生物膜-靶位”等多机制协同作用、环境介导的传播机制以及接合质粒介导的跨界耐药基因扩散等现象认识不足。本文旨在从“多机制协同”“基因水平转移-克隆传播-环境扩散”多维传播链等角度,对CRO的耐药机制与防治策略进行整合性综述,以期遏制CRO蔓延提供更全面的理论支持。

1 碳青霉烯耐药现状调查和分析

碳青霉烯类抗生素为非典型 β -内酰胺类抗生素,凭借其广谱抗菌活性与强效杀菌作用^[1],已成为治疗多重耐药革兰阴性菌感染的“最后防线”药物之一。CRO指对亚胺培南、美罗培南等药物耐药的革兰阴性杆菌。近年检出的CRO主要有碳青霉烯耐药肺炎克雷伯菌(carbapenem-resistant *Klebsiella pneumoniae*, CRKP)、碳青霉烯耐药鲍曼不动杆菌(carbapenem-resistant *Acinetobacter baumannii*, CRAB)、碳青霉烯耐药铜绿假单胞菌(carbapenem-resistant *Pseudomonas aeruginosa*, CRPA)等。

2024年,世界卫生组织将CRAB与碳青霉烯耐

药肠杆菌目列为“关键优先级”病原体,CRPA则为“高优先级”病原体^[2]。根据近十年的监测数据^[3,4],CRAB对碳青霉烯类抗生素的耐药率持续处于高位,从2014年的57%略降至2023年的55.5%,但形势仍然不容乐观。同期,CRKP的流行率也在全球范围内呈现快速上升趋势,其耐药率从2014年的6.4%上升到2023年的10.8%;在ICU等重点科室,由于患者病情危重、抗菌药物暴露频繁,CRKP耐药率通常显著高于平均水平。CRPA对碳青霉烯类抗生素的耐药率则呈现一定波动,2023年为16.3%,虽较2014年下降了约9%,耐药率仍处于较高水平。

CRO菌株呈现多重耐药甚至广泛耐药表型,导致绝大多数常规抗菌药物疗效受限。监测数据显示,CRKP对第三代头孢菌素(如头孢曲松)和氟喹诺酮类药物(如环丙沙星)的耐药率已超95%,对氨基糖苷类(如阿米卡星、庆大霉素)和磺胺甲恶唑-甲氧苄啶的耐药率也普遍较高,常介于70%~90%之间^[3]。在耐药基因型方面,CRKP以携带 bla_{KPC-2} (约85%)和 bla_{NDM} (约15%)为主,且这些基因型常与ST167等高危克隆相关联,其传播机制进一步加剧了耐药演变。而在肠杆菌目中,同时携带 bla_{NDM} 及 $bla_{OXA-48-like}$ 基因的双产酶菌株,对氨曲南-阿维巴坦的耐药率可高达57.1%^[5]。尽管多黏菌素、替加环素等总体耐药率目前仍维持在较低水平,但其临床应用面临着诸多挑战:多黏菌素肾毒性与神经毒性

显著,替加环素则血药浓度偏低,不适用于菌血症等严重感染。综上表明,即使新型治疗方案也正面临严峻挑战^[5,6]。

近年研究显示,碳青霉烯耐药菌不仅局限于医院环境,还通过污水系统向环境扩散^[7]。我国耐碳青霉烯类高毒力肺炎克雷伯菌感染率呈上升趋势,且存在显著的地域差异:浙江(28.5%)、江苏(19.4%)、北京(9.7%)为高发区,河南、山东、河北次之^[8]。除污水传播外,CRO的扩散还涉及土壤传播、动物-人间跨物种传播、国际旅行与贸易带来的跨境传播以及农产品供应链等多种途径,已成为复杂的公共卫生挑战。碳青霉烯耐药率居高不下且呈持续扩散之势,现有抗菌压力与临床干预尚不足以阻断其播散,因此深入探究碳青霉烯耐药的机制具有十分重要的科学和现实意义。

2 CRO的耐药机制

CRO的耐药机制主要包括产碳青霉烯酶水解、外膜孔蛋白突变、外排泵过表达(图1)、生物膜的形成及细菌靶位改变,这些机制常协同作用,导致高水平耐药。

2.1 产碳青霉烯酶

产碳青霉烯酶是CRO最主要的耐药机制^[9]。碳青霉烯酶是一类能够高效水解碳青霉烯类抗生素

的 β -内酰胺酶。根据氨基酸序列的相似性和活性中心的结构特征, β -内酰胺酶可分为A、B、C和D四类,碳青霉烯酶主要来源于其A、B、D三类;传统上,碳青霉烯酶并不包括C类 β -内酰胺酶,然而某些C类 β -内酰胺酶的突变体如CMY-10、CMY-19和CMY-37具有碳青霉烯水解能力^[10]。

A类 β -内酰胺酶中 bla_{KPC} 基因编码的碳青霉烯酶最具临床显著性^[11],这类酶能够水解青霉素类、头孢菌素类、碳青霉烯类等抗生素,其活性可被 β -内酰胺酶抑制剂抑制。B类 β -内酰胺酶由多种金属 β -内酰胺酶(metallo- β -lactamase, MBL)组成^[12],分为三个亚类(B1、B2和B3),其中B1亚类构成临床主要流行类型^[13],包括耐亚胺培南酶(IMP)、维罗纳整合子编码的金属 β -内酰胺酶(VIM)和新德里金属 β -内酰胺酶(NDM)。在鲍曼不动杆菌中,产生OXA-23、OXA-58等D类酶是其主要耐药机制^[14];此外,还有少部分菌株产NDM^[15]或VIM^[16]。D类 β -内酰胺酶中OXA家族占据主导地位,该家族成员中仅OXA-23、OXA-40、OXA-48及其衍生变异体(如OXA-162、OXA-181、OXA-232)具备碳青霉烯水解活性^[17]。OXA-48型作为该家族的核心耐药基因^[11],通过质粒介导的水平基因转移与突变在肠杆菌目细菌中传播,已成为引起多重耐药革兰阴性菌感染的关键因素之一。

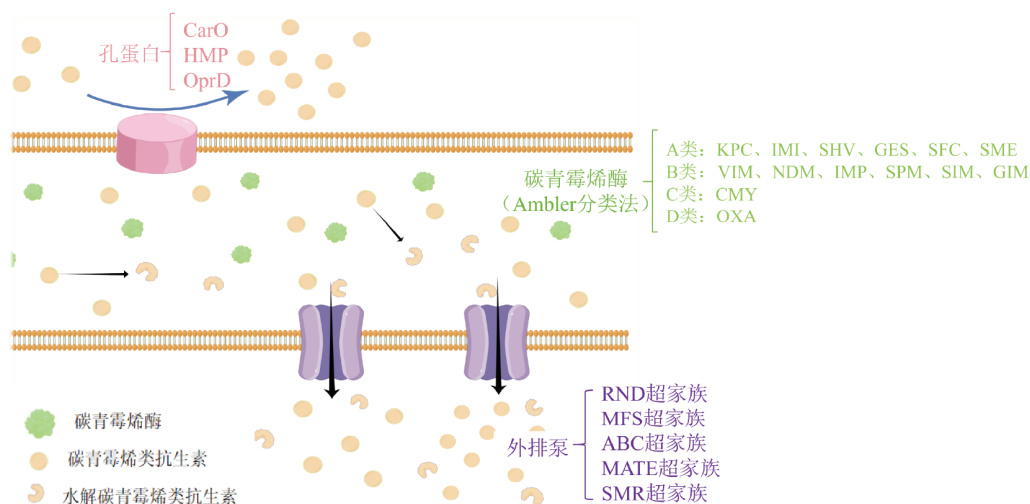


图1 CRO的耐药机制

KPC:肺炎克雷伯菌碳青霉烯酶;IMI:亚胺培南水解 β -内酰胺酶;GES:圭亚那超广谱 β -内酰胺酶;SFC:居泉沙雷菌碳青霉烯酶;SME:黏质沙雷菌碳青霉烯酶;SHV:巯基可变型 β -内酰胺酶;VIM:维罗纳整合子编码酶;NDM:新德里金属内酰胺酶;IMP:耐亚胺培南碳青霉烯酶;SPM:圣保罗金属酶;SIM:首尔亚胺培南酶;GIM:德国亚胺培南酶;CMY:头孢菌素酶;OXA:苯唑西林酶。

Figure 1 Drug resistance mechanism of CRO

另外,虽然超广谱 β -内酰胺酶(extended-spectrum beta-lactamases, ESBLs)如CTX-M-15、TEM、SHV和AmpC酶本身对碳青霉烯类抗生素的水解能力很弱,但当它们与其他机制共存时,会显著降低细菌对碳青霉烯类的敏感性,导致治疗难度上升,例如肺炎克雷伯菌中ESBL或AmpC的产生、孔蛋白缺失以及外排泵过度活跃的综合效应,可共同介导对厄他培南的耐药^[18]。窄食单胞菌G4菌株基因组编码ESBLs基因、脂多糖修饰基因和多个外排泵基因,从而对美罗培南和多黏菌素高度耐药^[19]。表1列出了主要碳青霉烯酶分类及其代表酶。

2.2 外膜孔蛋白突变

孔蛋白(outer membrane protein, Omp)是碳青霉烯类抗生素进入革兰阴性杆菌细胞的主要通道,其表达下调或缺失可在不同程度降低膜通透性,导致耐药。例如在肠杆菌目细菌中, OmpK35和OmpK36缺失导致对厄他培南的耐药性增加^[38]。此外,抗生素使蛋白结构发生变化也能影响药物与靶点的相互作用。如OprD孔蛋白的突变导致了CRPA耐药性^[39], OmpK36的截短突变使得细菌对美罗培南、亚胺培南的耐药性进一步增强^[40]。

细菌还可能产生新的蛋白来替代或补充被抗菌药物抑制的蛋白质功能。例如当肺炎克雷伯菌

OmpK36缺失时,其可能通过上调其他孔蛋白的表达以维持基本的物质交换^[41]。在某些情况下,细菌可能会完全停止表达某些孔蛋白以限制药物内流。这种机制常与 β -内酰胺酶的产生等其他耐药机制共同作用,形成多重耐药性。例如,在CRKP中,孔蛋白突变可与酶水解机制协同,形成高效的多重耐药屏障^[18]。

2.3 外排泵过表达

外排泵能够通过主动运输的方式将药物从胞内泵出胞外,从而降低药物浓度至有效治疗浓度以下。根据能量来源可将外排泵分为RND、MSF、ABC、SMR和MATE五类,碳青霉烯类外排泵主要集中在RND家族(如MexAB-OprM、AdeABC和AcrAB-TolC)。

不同菌属的外排泵系统存在差异,鲍曼不动杆菌的外排泵系统多为AdeABC, *adeB*高表达与碳青霉烯耐药相关, *adeG*的过表达能促进生物膜形成^[42],二者协同加剧耐药。研究表明在没有携带碳青霉烯酶耐药基因的条件下, MexAB-OprM外排泵过表达是铜绿假单胞菌对美罗培南产生耐药的主要机制^[43]。通过结构生物学和抑制剂筛选,研究发现AdeB的底物结合口袋可直接识别碳青霉烯类抗生素^[44],为开发外排泵抑制剂提供了靶点。

表1 主要碳青霉烯酶分类及代表酶
Table 1 Classification of major carbapenemases and representative enzymes

Ambler分类	酶类型	具体酶名称	主要水解底物	参考文献
Class A	丝氨酸碳青霉烯酶	肺炎克雷伯菌碳青霉烯酶(KPC)	所有 β -内酰胺类(青霉素、头孢菌素、碳青霉烯类)	[20]
		亚胺培南水解 β -内酰胺酶(IMI)	碳青霉烯类,弱水解头孢菌素	[21]
		圭亚那超广谱 β -内酰胺酶(GES)	GES-1~GES-5水解广谱头孢菌素;GES5~GES6水解碳青霉烯类	[22]
		居泉沙雷菌碳青霉烯酶(SFC)	碳青霉烯类,头孢他啶	[23]
		黏质沙雷菌碳青霉烯酶(SME)	碳青霉烯类,头孢他啶	[24]
		巯基可变量 β -内酰胺酶(SHV)	青霉素+早期头孢菌素,碳青霉烯类	[25]
Class B	金属- β -内酰胺酶(MBLs)	维罗纳整合子编码酶(VIM)	所有 β -内酰胺类(包括碳青霉烯),但对单环酰胺类(如氨基糖苷)无活性	[26]
		新德里金属内酰胺酶(NDM)		[27]
		耐亚胺培南碳青霉烯酶(IMP)		[28]
		圣保罗金属酶(SPM)		[29]
		首尔亚胺培南酶(SIM)		[30]
		德国亚胺培南酶(GIM)		[31]
Class C	头孢菌素酶(CMY)	CMY-10	头孢菌素类(尤其第三代如头孢噻肟、头孢他啶);合并孔蛋白缺失	[32]
		CMY-19		[33]
		CMY-37		[34]
Class D	苯唑西林酶(OXA)	OXA-48	苯唑西林、碳青霉烯类,弱水解广谱头孢菌素	[35,36]
		OXA-40	碳青霉烯类,苯唑西林	[37]
		OXA-23	碳青霉烯类,苯唑西林	[14]

2.4 “酶-孔蛋白-外排泵”的协同作用

碳青霉烯的高水平耐药源于多种耐药机制的协同作用,同时其也是导致广泛耐药和多重耐药的关键。外膜孔蛋白缺失或突变大幅减少药物内流,使得低水平水解酶即可生效,同时外排泵的过表达进一步清除残余药物。多重耐药基因常共存于同一质粒,使单一协同机制作用于多类抗生素耐药。这种协同效应常导致广泛的药物失效。在肺炎克雷伯菌中,外膜上的孔蛋白(OmpK35、OmpK36)表达下调的同时增强外排泵活性,与碳青霉烯酶(如KPC-2)相结合,共同构成“外膜孔蛋白缺失-外排泵激活-酶水解”三位一体耐药闭环,导致碳青霉烯类药物的不可逆耐药^[18,45]。

2.5 促进生物膜形成

生物膜的形成是驱动细菌对碳青霉烯类药物产生高度耐药性的关键因素。生物膜通过建立物理屏障、改变细菌生理状态以及促进耐药基因传播等多种机制,保护内部细菌免受抗生素作用,导致难以根除的顽固性感染。

生物膜形成物理屏障可限制抗生素进入胞内,与其他耐药机制协同作用增强耐药性。研究证明生物膜态细菌对亚胺培南和美罗培南的最小抑菌浓度(minimum inhibitory concentration, MIC)均显著上升,同时基质中的环境DNA(eDNA)通过与金属离子螯合,并与碳青霉烯酶共同作用,进一步增强耐药性^[46]。生物膜内部存在明显的营养和氧气梯度,深层区域因营养和氧气匮乏,导致细菌生长缓慢或进入休眠状态,其细胞壁合成需求降低,从而造成碳青霉烯类抗生素耐药^[47]。生物膜形成能力与碳青霉烯耐药性呈显著正相关,高密度菌群极大地促进了质粒/转座子介导的碳青霉烯酶耐药基因(如 bla_{KPC} 、 bla_{NDM} 、 bla_{VIM} 、 bla_{OXA-48} ,尤其是 bla_{NDM})的水平转移或高表达。例如,鲍曼不动杆菌通过群体感应调控的胞外多糖-eDNA网络,增强生物膜致密性,限制碳青霉烯渗透的同时,还能诱导 bla_{OXA-48} 基因高表达,增强碳青霉烯耐药^[48]。在强生物膜形成菌株中,群体感应基因(如 $luxS$)的表达水平显著高于弱或无生物膜形成能力的菌株。在广泛耐药肺炎克雷伯菌中,生物膜形成、碳青霉烯酶基因表达及群体感应调控三者协同提升了碳青霉烯耐药性^[49]。

2.6 细菌靶位改变

青霉素结合蛋白(penicillin-binding proteins,

PBPs)作为碳青霉烯类抗生素作用的核心靶点,其结构、表达量或亲和力的改变是介导细菌耐药的又一重要机制。PBPs发生突变或修饰可导致其与药物结合效率下降,进而显著降低细菌对碳青霉烯类抗生素的敏感性。例如,在铜绿假单胞菌中,编码PBP3的 $ftsI$ 基因发生特异性突变(如Phe533Leu),可直接导致其对美罗培南、多尼培南等碳青霉烯药物的敏感性降低至原来的1/8~1/2^[50]。

然而,靶位改变极少单独导致高水平耐药,其更深层的临床意义在于与“酶水解-孔蛋白缺失-外排泵过表达”等经典机制形成多维度、协同增效的耐药网络。这一效应在ST2型CRAB菌株中尤为典型:该菌株不仅同时表达OXA-23和OXA-66碳青霉烯酶,PBP3发生突变(K235N/H370Y),还显示出外排泵(如AdeABC)的过表达,多种机制共同作用从而加剧耐药。其中,PBP3的H370Y突变被确定为对新型药物头孢德罗耐药的关键标志^[51]。因此,未来针对CRO的联合治疗策略或新型抗菌药物研发,应考虑将恢复PBP靶点敏感性作为潜在方向之一。

3 CRO的传播与扩散

碳青霉烯耐药性的全球蔓延是一个由分子机制与宏观传播共同驱动的过程。产碳青霉烯酶及外排泵过表达构成耐药的分子基础,而耐药性的扩散则主要依赖于基因水平转移和耐药克隆的全球传播。研究表明,亚抑菌浓度的抗生素、重金属或其他污染物可显著上调接合转移相关基因表达,促进耐药基因在不同细菌间传播。

3.1 基因水平转移

基因水平转移是CRO耐药性扩散的核心途径,其效率受种属、基因元件类型(质粒、转座子、整合子)以及环境压力等因素影响。基因水平转移途径主要包括接合、转化以及转导。碳青霉烯耐药关键基因主要依赖接合质粒、转座子和整合接合元件(integrative and conjugative element, ICE)转移到其他细菌,四大病原体均出现新型耐药机制且存在明显属间差异:CRAB以克隆扩张为主,而肠杆菌目更依赖质粒的水平转移,这一发现为物种特异性防控策略的制定提供了依据。此外,本课题组在金黄杆菌POL2菌株^[52]和约氏不动杆菌M19菌株^[53]中鉴别出可以传播碳青霉烯耐药的ICE和新型转座子,表明环境微生物中也存在广泛的碳青霉烯耐药转移。

表2列出了主要CRO病原体的流行病学特征、耐药机制与传播能力。

在基因水平转移过程中,ICE是主要的传播载体。处于休眠状态的染色体整合型ICE被激活后,首先从宿主染色体上切除并形成环状DNA中间体。该环状分子经松弛酶切割后产生单链转移DNA(T-DNA),T-DNA通过接合孔转运至受体菌。在受体菌内,该单链DNA作为模板合成其互补链,形成完整的双链ICE并重新整合至染色体,使受体菌转变为潜在的新供体,从而完成水平基因转移的传播循环(图2)。

环境压力可显著加速这一过程。DNA损伤剂(如消毒剂、抗生素)会触发细菌SOS应急响应,通过RecA-LexA通路上调接合转移基因表达,促进耐药基因水平转移。近期研究表明,医院污水中的次氯酸钠消毒剂可激活细菌SOS应急响应,促使携带*bla*_{NDM-5}的质粒通过粪肠球菌载体向16个细菌门的菌株发生跨界转移,其中外排泵高表达菌株(如肺炎克雷伯菌ST15)因消毒剂耐受性增强更易捕获质粒,从而加速碳青霉烯耐药基因的环境传播。

除消毒剂外,亚抑制浓度的碳青霉烯类抗生素

也可触发SOS应急响应,当携带*bla*_{NDM-1}的质粒缺失SOS抑制基因时,其在大肠埃希菌中的接合转移效率可提高2~4倍^[68]。这表明抗生素的使用非但未能有效清除耐药菌,反而可能直接促进其耐药性的扩散。

3.2 耐药克隆的传播与扩散

除水平转移,具有竞争优势的耐药克隆也可通过垂直传播在全球范围扩散。这些优势克隆通常兼具多重耐药性、较强的环境适应性和一定的毒力,使其能够在压力环境中持续存在并传播。例如,肺炎克雷伯菌ST11克隆是我国及亚洲地区CRKP感染的主导克隆型^[69],其进化分支ST11-KL64(Clade E)表现出增强的抗吞噬能力和生长竞争优势^[54],其进化部分促进了毒力质粒(如*rmpA2*阳性质粒)和耐药基因的获取;在欧美地区,ST258则是经典的流行高危克隆^[70]。鲍曼不动杆菌IC2(ST2)克隆则在全球广泛传播,检出率持续居高^[61]。这些克隆菌株通过患者转院、国际旅行、医疗交流等途径,实现跨地区甚至跨国界的传播。

3.3 医院及环境中的传播与感染控制

碳青霉烯耐药菌的接触传播途径较为复杂,涉

表2 主要CRO病原体的流行病学特征、耐药机制与传播能力

Table 2 Epidemiology, resistance mechanisms, and transmission capacity of major CRO pathogens

CRO	检出率及趋势	主要耐药机制	水平转移能力	临床意义与主要流行克隆型
肺炎克雷伯菌(CRKP)	中国2023年CRKP检出率:10.8%(碳青霉烯类) ^[3] ;ICU病区:38.6% ^[54]	碳青霉烯酶产生:KPC-2(85%)、NDM(15%) ^[55] ;新发现:插入序列介导的荚膜相变可同时增强耐药质粒接合转移效率、环境适应性和毒力恢复能力 ^[56]	强: <i>bla</i> _{KPC} 、 <i>bla</i> _{NDM} 基因位于IncFII、IncX3质粒;ST11-KL64显示更强的重组能力 ^[57]	ST167:在环境-临床传播链中占比上升 ^[58] ;高毒力CRKP:流行增加,多与ST11-KL64相关,携带 <i>rmpA</i> 、 <i>rmpA2</i> 等毒力基因,致死率高 ^[57] ;ST11-KL64(Clade E):病死率54.5%(血液感染) ^[54] ;ST258:主要在欧美流行 ^[59]
鲍曼不动杆菌(CRAB)	中国2023年CRAB检出率:55.5%(碳青霉烯类) ^[3] ;中国制药环境:携带 <i>bla</i> _{NDM-1} 质粒的菌株检出 ^[60]	碳青霉烯酶产生:主要产生OXA型酶;膜蛋白变异:OmpA、CarO缺失 ^[61] ;外排泵:AdeABC过表达 ^[61]	中等:耐药基因 <i>bla</i> _{OXA-23} 由转座子(ISAbal)传播	STPas2(ST2):全球主导克隆(非洲40.4%,欧洲83.9%,北美71%) ^[61] ;ST208:东亚高发(13.1%) ^[61]
大肠埃希菌(CREC)	中国2023年CREC检出率:7%(碳青霉烯类) ^[3] ;新加坡NDM-CPE:氨曲南-阿维巴坦耐药率18.8%(大肠埃希菌) ^[55] ;双产酶株耐药率:57.1%(NDM、OXA-48) ^[55]	碳青霉烯酶产生:NDM-5(主导)、KPC-2;联合机制:PB3插入突变(如Tyr-333-YRIK)联合CMY型AmpC酶,导致新型酶抑制剂复合制剂耐药 ^[55]	极强: <i>bla</i> _{NDM-5} 位于可接合质粒,接合效率>10 ⁻² ;高危克隆:ST361(双产酶株,0-5 SNP差异) ^[55]	ST361:新加坡暴发克隆,与高耐药率相关 ^[55] ;ST167:中国CREC的主要流行株,其中KpnK48亚克隆占比最高,是我国CREC快速传播的关键克隆 ^[62] ;ST131:全球性流行克隆 ^[63]
铜绿假单胞菌(CRPA)	中国2023年CRPA检出率:16.3%(碳青霉烯类) ^[3]	膜孔蛋白缺失或改变(如OprD缺失/失活,主要机制) ^[64] ;外排泵:MexAB-OprM过表达(传统机制)	强: <i>bla</i> _{VIM} 、 <i>bla</i> _{IMP} 基因位于I类整合子;环境因素可增强接合效率 ^[65]	ST235、ST111:国际高风险克隆,常与金属酶基因相关 ^[66] ;ST277:主要在巴西等拉丁美洲国家流行;ST463:中国东部地区的优势地方克隆型(MLST分型) ^[67]

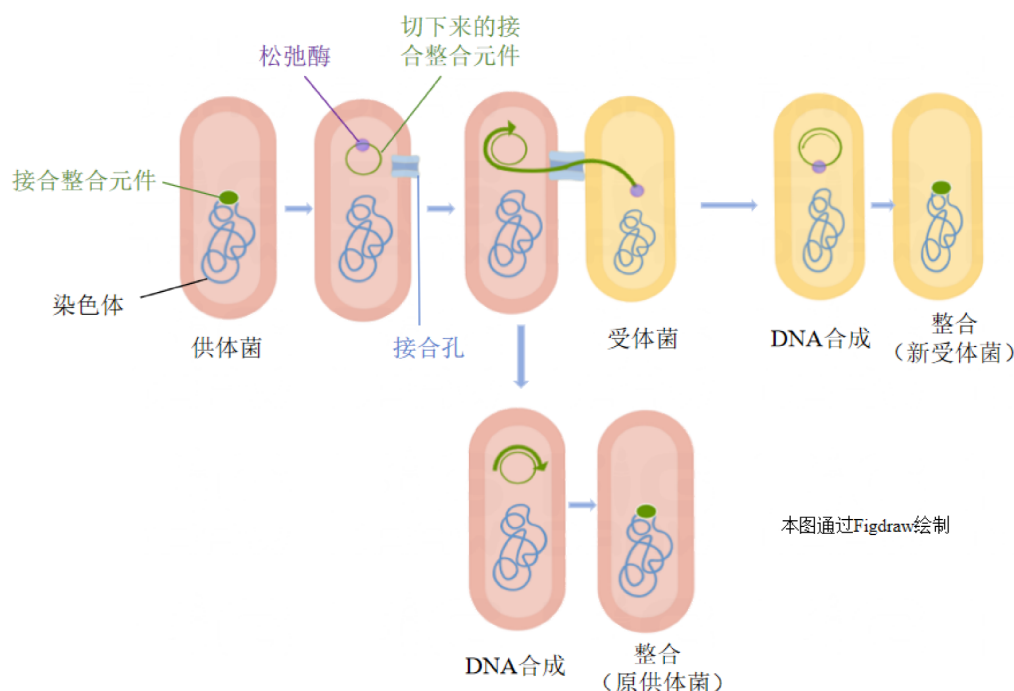


图2 接合转移过程

Figure 2 The conjugation process

及临床、农业、养殖业等多重环节。接触传播是院内感染的主要方式,患者通过接触污染的医疗设备(如呼吸机、导管)、医护人员手部或医院环境(如床栏、水槽)感染CRO。医院感染控制措施的不足,如手卫生依从性低、隔离措施执行不到位、环境清洁消毒不彻底及主动监测筛查缺失等,为克隆菌株的交叉传播创造了条件,最终导致院内感染的暴发^[7]。同时该研究还证实碳青霉烯耐药基因可通过医疗废水排放进入城市水系统,并在医院与环境中双向传播:携带 bla_{KPC-2} 的高风险ST11-KL64型碳青霉烯耐药高毒力肺炎克雷伯菌克隆在医院ICU、污水处理厂及邻近河流中持续存在,且其对紫外线消毒具有显著高于其他克隆的耐受性^[69],这种对多种环境压力的抵抗能力,极大增加医院感染控制的难度。而污水处理厂对耐药菌的清除不足,进一步加剧了耐药基因通过水体接触向社区传播的风险^[7]。

4 CRO的防治策略与现状

面对日益严峻的CRO感染形势,当前的防治策略已从传统的抗生素联用向多维度、协同干预的方向发展,涵盖新型药物研发、耐药机制靶向干预和新技术应用等多个方面。

4.1 CRO主动筛查

主动筛查是遏制CRO耐药菌院内传播的核心策略之一^[71]。规范的筛查流程涵盖采样、检测与鉴定多个环节。临床常用直肠拭子作为采样方式,并应用选择性培养基培养、PCR及免疫层析等技术进行快速鉴定。基于PCR的分子诊断技术可在数小时内实现碳青霉烯酶基因的快速分型,其检测范围通常覆盖了全球及地区流行的关键基因型,主要包括在肠杆菌目中最常见的 bla_{KPC} 、在鲍曼不动杆菌中占主导的 $bla_{OXA-23/48/51-like}$,以及日益重要的金属 β -内酰胺酶基因,如 bla_{NDM} 、 bla_{IMP} 和 bla_{VIM} 等,为后续精准隔离与治疗提供关键依据^[69]。

多项研究表明,将主动筛查纳入感染控制体系可显著降低CRO的交叉传播风险。筛查阳性者应立即实施接触隔离措施,包括单间隔离、严格执行手卫生、使用专用诊疗设备及强化清洁消毒等。实践表明,该策略不仅能有效延缓耐药菌传播,也有助于优化抗菌药物的使用,最终改善患者预后^[7,69]。因此,在CRO高流行病房或暴发流行期间,实施以主动筛查为基础的综合干预,是构建医院耐药菌感染防控体系中不可或缺的一环。

4.2 现有临床治疗策略

目前,针对CRO感染的临床治疗以多药联合为

主,治疗方案取决于病原体的耐药表型和感染部位。对于产KPC或OXA-48-like等丝氨酸碳青霉烯酶的肠杆菌目菌株,新型酶抑制剂复方制剂如头孢他啶-阿维巴坦、美罗培南-法硼巴坦和亚胺培南-西司他丁-瑞来巴坦疗效显著,是诸多指南推荐的首选药物^[72]。头孢德罗作为铁载体头孢菌素,对多种碳青霉烯酶具有广谱活性,为多重耐药菌感染提供了重要后备选择^[73],但其对产NDM-5的大肠埃希菌耐药率较高,且与ST167高危克隆密切相关^[27],也具有一定局限性。

对于产NDM、VIM等金属 β -内酰胺酶的菌株,目前仍以多黏菌素、替加环素或氨基糖苷类为基础,联合碳青霉烯类药物以提高疗效^[74]。但此类方案毒副作用较大且疗效不尽如人意,凸显了对新型抑制剂的迫切需求。

4.3 酶抑制剂

针对MBL的抑制剂研发已成为当前热点。新型金属酶抑制剂能竞争性结合 bla_{NDM-1} 的双锌核活性中心,显著降低细菌耐药性^[75]。二氢苯并咪唑类抑制剂17u的双位点结合机制可完全阻断金属酶的水解功能,使亚胺培南对 bla_{NDM-1} 阳性菌的MIC降低至原来的1/128,其效果显著优于传统抑制剂^[76]。针对现有 β -内酰胺酶抑制剂无法覆盖MBL的难题,他伏硼罗(tavaborole)的“老药新用”的策略能够抑制A、B类碳青霉烯酶,联合美罗培南在模型中实现100%生存率及器官细菌载量清零,为多重耐药革兰阴性菌感染提供了新型联合治疗方案^[77]。

4.4 外排泵抑制剂

尽管外排泵抑制剂尚未广泛应用于临床,但作为恢复抗生素敏感性的潜在策略,仍是基础研究的热点。研究表明,新型抑制剂MBX-4191通过结合AcrB蛋白的变构位点阻断药物外排,能够显著降低药物的MIC^[78]。胡椒碱则通过抑制铜绿假单胞菌的MexAB-OprM外排泵阻断药物外排通道,与亚胺培南联用时可增强抗菌活性。本团队在中药化合物库中筛选出的 α -侧柏酮能通过特异性抑制碳青霉烯专一耐药ABC外排泵,与美罗培南协同作用功效明显。然而,外排泵抑制剂的特异性和潜在毒性限制了临床应用,未来需开发更具选择性的分子。

4.5 其他防治策略

噬菌体-CRISPR协同系统展现出了精准的抗菌

潜力。该系统结合了噬菌体的特异性感染能力与CRISPR-Cas系统的基因编辑功能,为实现耐药菌的精准靶向和耐药性逆转提供了新策略。例如,特异性靶向KPC酶的噬菌体可穿透生物膜基质,恢复其对亚胺培南的敏感性^[79]。基于CRISPR-Cas9的基因编辑技术通过靶向降解 bla_{NDM-1} 等耐药基因,成功构建了CRKP中特定基因的敲除株和突变株,以验证这些基因在细菌抗吞噬能力及进化中的作用^[54]。

另一方面,联合用药策略通过多靶点协同作用增强抗菌疗效。磷霉素与 β -内酰胺类药物联用可同时破坏细胞壁合成与胞内代谢,已在部分临床试验中展示出良好效果^[80,81]。新型 β -内酰胺酶抑制剂复方制剂如舒巴坦-杜洛巴坦针对CRAB具有显著活性,已被批准用于临床^[76]。

5 结语与展望

“酶-孔蛋白-外排泵-生物膜-靶位”的多维协同耐药,与“基因水平转移-克隆扩张-环境扩散”的立体传播网络,共同构成了当前CRO危机的核心。未来的防治策略必须基于对这种“协同-立体”模式的深刻理解,发展多靶点、跨学科的新型干预手段、优化抗生素使用和推动新型抗菌药物开发,有望为遏制CRO全球蔓延提供突破性解决方案。

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