Advances in Clinical Medicine 临床医学进展, 2025, 15(4), 2116-2123
Published Online April 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1541161

Hans汉斯

肺炎克雷伯菌多黏菌素耐药机制新进展

周梦雨[1]，赵冬冬[2*]

[1]浙江大学医学院，浙江 杭州
[2]浙江大学医学院附属邵逸夫医院感染科，浙江 杭州

收稿日期：2025年3月18日；录用日期：2025年4月11日；发布日期：2025年4月18日

摘 要

全球范围内细菌耐药性的上升给临床诊疗带来了挑战。碳青霉烯耐药肺炎克雷伯菌(CRKP)的流行使得医院获得性感染率增加，对患者的治疗方案变得有限，同时增加了住院时间、死亡率和费用。多黏菌素则重新回到了临床，成为对抗革兰阴性多重耐药菌的最后一道防线。不幸的是，全球范围内陆续出现多黏菌素耐药的肺炎克雷伯菌。本文综述了肺炎克雷伯菌耐药机制的新进展，包括染色体介导的耐药机制和质粒介导的耐药机制。此外，本文还探讨了异质性耐药、生物膜屏障效应等新发现的耐药机制。通过系统分析近年研究，本文旨在为肺炎克雷伯菌多黏菌素耐药机制解析和新型抗感染策略开发提供理论依据。

关键词

肺炎克雷伯菌，多黏菌素耐药机制，脂多糖修饰，染色体突变，*mcr*基因

New Advances in the Mechanisms of Colistin Resistance in *Klebsiella pneumoniae*

Mengyu Zhou[1], Dongdong Zhao[2*]

[1]School of Medicine, Zhejiang University, Hangzhou Zhejiang
[2]Department of Infectious Diseases, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou Zhejiang

Received: Mar. 18th, 2025; accepted: Apr. 11th, 2025; published: Apr. 18th, 2025

Abstract

The increasing prevalence of bacterial drug resistance worldwide has posed significant challenges to clinical diagnosis and treatment. The emergence of carbapenem-resistant *Klebsiella pneumoniae*

*通讯作者。

文章引用: 周梦雨, 赵冬冬. 肺炎克雷伯菌多黏菌素耐药机制新进展[J]. 临床医学进展, 2025, 15(4): 2116-2123.
DOI: 10.12677/acm.2025.1541161

(CRKP) has led to an increase in hospital-acquired infection rates, limited treatment options for patients, and increased hospital stays, mortality, and costs. Colistin has re-emerged in the clinical setting as the last line of defense against multidrug-resistant Gram-negative bacteria. Unfortunately, strains of colistin-resistant *K. pneumoniae* have been reported globally. This review summarizes the latest progress in the resistance mechanisms of *K. pneumoniae*, including chromosomally mediated resistance mechanisms and plasmid-mediated resistance mechanisms. Additionally, this article discusses newly discovered resistance mechanisms such as heterogeneous resistance and biofilm barrier effects. By systematically analyzing recent studies, this review aims to provide a theoretical basis for the elucidation of colistin resistance mechanisms in *K. pneumoniae* and the development of novel anti-infective strategies.

Keywords

***Klebsiella pneumonia*, Colistin Resistance Mechanisms, Lipopolysaccharide Modification, Chromosomal Mutations, *mcr* Genes**

1. 引言

全球多重耐药革兰阴性杆菌的增加，对人类健康构成越来越大的威胁，并造成了重大的医疗卫生负担[1]。在这些耐药菌中，肺炎克雷伯菌(*Klebsiella pneumoniae*)因其强大的耐药性和致病性，尤其值得关注。肺炎克雷伯菌是一种不运动的、杆状革兰阴性菌，作为重要的院内感染病原体，肺炎克雷伯菌常见的感染部位包括尿路、下呼吸道、胆道和手术伤口，常导致包括肺炎、菌血症、尿路感染、胆囊炎、脑膜炎、肝脓肿等疾病[2]-[4]。近年来，随着住院患者中谱抗生素的广泛使用，肺炎克雷伯菌的耐药性显著增加，尤其是碳青霉烯耐药肺炎克雷伯菌的出现，使其成为院内感染的重要致病菌，对患者的健康和医疗安全构成了严重威胁[5]。根据中国 CHINET 细菌耐药监测网数据(http://www.chinets.com/Chinet)显示，肺炎克雷伯菌对碳青霉烯类抗生素的耐药率从 2015 年的 15.6%上升至 2024 年的 23.4%。因此，为了应对这一情况，一种已被淘汰的抗生素——多黏菌素——重新回到了人们的视野中[6]。

多黏菌素是一类由多黏类芽孢杆菌产生的环寡肽抗菌药物，其中多黏菌素 B 和黏菌素(多黏菌素 E)是最常被应用的两种多黏菌素类药物。由于多黏菌素的肾毒性和神经毒性，以及各种新的有效抗生素的发现，多黏菌素在 20 世纪 70 年代逐渐被放弃[7]。直到 20 世纪 90 年代，碳青霉烯类耐药革兰阴性菌的全球流行，使得重新成为治疗多重耐药革兰阴性菌的最后手段[8]。而在头孢他啶/阿维巴坦等新型 β-内酰胺酶抑制剂组合、MRX-8 等新型多黏菌素类抗菌药物发展迅速的现在，多黏菌素作为“最后防线”的绝对地位虽被新型药物部分取代，但在金属酶介导的耐药菌感染、血液病及免疫抑制患者的严重感染及经济受限场景中仍不可替代，其临床应用成为多重耐药菌“精准防线”的一部分，与其他药物共同应对耐药挑战。

不幸的是，由于人类及动物中多黏菌素的滥用及误用，全球范围内迅速出现了多黏菌素耐药的病原体，部分区域的耐药率甚至超过 10% [9] [10]。这一现象引起了全球医学界的广泛关注，因为耐药机制的复杂性使得临床治疗面临更大的挑战。研究表明，多黏菌素耐药机制主要包括染色体突变和质粒介导的基因水平转移，还涉及生物膜形成、异质性耐药等新维度。其中，质粒介导的多黏菌素耐药性的出现，尤其让人对未来医药环境产生担忧[11]。

综上所述，多黏菌素耐药机制的研究对于临床治疗和药物研发具有重要的指导意义。本文将聚焦近年来多黏菌素耐药机制的研究进展，包括染色体突变、质粒介导的基因水平转移、异质性耐药、生物膜形成等方面，以期为临床医生提供更精准的治疗策略，同时也为新型抗菌药物的研发提供理论依据。

2. 染色体介导的耐药机制

2.1. 双组分调节系统的调控

在肺炎克雷伯菌中，多黏菌素耐药由多种策略介导，其分子调控机制主要与参与 LPS 修饰途径的基因突变有关。有研究表明，与野生型肺炎克雷伯菌的 LPS 相比，来自耐多黏菌素菌株的 LPS 对多黏菌素 B 和黏菌素的结合亲和力低约 5 倍[12]。参与细菌信号转导和应激反应的一种普遍形式称为双组分调控系统[13]-[15] (two-component regulatory systems, TCS)，是细菌中一种普遍存在的信号转导和应激反应机制。在肺炎克雷伯菌中，多黏菌素耐药受 PhoPQ、PmrAB、CrrAB 双组分系统调控，包括这些 TCS 的调控因子，比如 *pmrD* 基因、*mgrB* 基因。

PmrAB 以及 PhoPQ 双组分调控系统通常在低 pH、高 Fe^{3+}、低 Ca^{2+}、低 Mg^{2+}离子的环境下被激活，分别通过编码 4-氨基-4-脱氧-L-阿拉伯糖(L-Ara4N)和磷酸乙醇胺(PEA)来修饰脂质 A，前者可将脂质 A 的净负电荷改变为中性电荷[16]，后者则将脂质 A 的净负电荷从−1.5 增加到−1。通过提供了额外的阳离子基团，中和 LPS 整体负电荷，阻碍与多黏菌素的结合，导致其对多黏菌素的耐药[17]。研究表明，*pmrB* 的突变是导致多黏菌素耐药的主要机制之一。例如，T157P、G207D 和 T246A 等突变位点能够显著影响 *pmrB* 的结构和功能，进而导致耐药性[18]。

此外，还有一种 TCS 称为 CrrAB，被证实参与 LPS 修饰介导的多黏菌素耐药，与 PhoPQ 和 PmrAB 的双组分调控系统类似，可以感知环境阳离子浓度，并做出相应反应[19]-[21]。值得注意的是，CrrAB 系统本身与多黏菌素耐药无关，而是 CrrAB 基因的突变介导多黏菌素耐药[22]。CrrB 基因激活后，通过诱导 CrrC 基因(也称为 *H239_3062* 基因)表达上调，介导 PmrAB 系统过表达，*arnBCADTEF* 操纵子激活、*pmrC* 基因、*pmrE* 基因的表达，促进脂质 A 的修饰，进而导致多黏菌素耐药。研究表明，*crrB* 基因突变的临床肺炎克雷伯菌菌株相比 *mgrB* 突变、*pmrB* 或 *phoQ* 突变所致的多黏菌素耐药菌株，表现出高水平耐药(MIC ≥ 512 mg/L)，这可能与编码 RND 型外排泵的 *H239_3064* 基因的转录上调有关，导致菌株对多黏菌素、四环素、替加环素的耐药性增加[23]。

2.2. *mgrB* 基因失活

在肺炎克雷伯菌中，MgrB 作为 PhoPQ 系统的负调控因子，通过抑制 PhoQ 激酶的活性维持系统稳态，从而限制 LPS 修饰相关基因的过度表达。*mgrB* 的失活或功能缺失(包括插入序列插入、点突变或基因缺失)被认为是导致临床菌株对多黏菌素耐药性产生的最主要的分子机制[24] [25]。*mgrB* 基因发生突变时，可导致 PhoPQ 系统失去负反馈调节，导致 PhoQ 自磷酸化持续激活，进而上调 *arnBCADTEF* 操纵子，催化脂质 A 添加 L-Ara4N，使菌株产生多黏菌素耐药性[26]-[28]。研究显示，由插入序列(*IS5-like*、*IS1F*、*ISKpn13*、*ISKpn14*、*IS10R*)引起的 *mgrB* 基因突变是临床肺炎克雷伯菌对多黏菌素耐药的主要原因[29] [30]。这些插入元件通常来源于环境菌株或噬菌体，通过水平基因转移(HGT)在肺炎克雷伯菌种群中扩散，加速耐药表型的传播。

2.3. 脂多糖合成途径的适应性改变

脂多糖合成途径的适应性改变是肺炎克雷伯菌对多黏菌素耐药的机制之一。除 L-Ara4N 和 pEtN 修饰外，脂质 A 的羟化或酰化程度的改变也可显著影响多黏菌素的结合能力。研究表明，*lpxM* 基因的突

变会导致脂质 A 六酰化程度减少，进而降低外膜的通透性，减少多黏菌素与脂质 A 的结合。这种结构修饰不仅影响多黏菌素的结合，还可能通过改变细胞外膜的物理性质，进一步增强细菌的耐药性[31] [32]。

2.4. 荚膜多糖过表达

肺炎克雷伯菌表面的荚膜多糖(CPS)携带的负电荷，能够与阳离子抗生素(如多黏菌素)结合，通过负电荷捕获多黏菌素，形成物理屏障，从而阻止多黏菌素与脂多糖相互作用，从而减少细菌表面药物量，进而增强细菌耐药性[33]。质粒携带的 *rmpA*、*rmpA2* 等基因可介导荚膜多糖产生增加[34]，与荚膜合成(Rcs)磷酸转移系统也在耐药性中发挥作用[31]。Rcs 与 PhoPQ 之间存在交叉调控作用。突变体 *rcsB* 上调 PhoPQ 的表达，意味着 Rcs 系统通常下调 PhoPQ 系统，从而介导对多黏菌素的耐药性[35]，但其中的具体机制在多黏菌素耐药菌株中还有待进一步研究。

3. 质粒介导的多黏菌素耐药机制

3.1. *mcr* 基因家族的传播

2015 年 11 月，中国首次发现肠杆菌科细菌中质粒介导多黏菌素耐药基因，*mcr-1* 基因，这是第一次报道多黏菌素耐药性可通过水平基因转移[11]。携带 *mcr* 基因的质粒具有接合和转移能力，有助于多黏菌素耐药性的传播性、稳定性和持久性[48]。除了 *mcr-1*、*mcr-8* 基因外，在肺炎克雷伯菌中还报道了其他 *mcr* 同源基因(即 *mcr-3*、*mcr-7*、*mcr-9*、*mcr-10*) [36]-[38]。

mcr 基因编码磷酸乙醇胺－脂质 A 转移酶，通过与 PmrC 类似的途径，介导在细菌脂质 A 结构中加入磷酸乙醇胺，导致细菌外膜整体负电荷减少，从而降低与阳离子的多黏菌素的亲和力，导致菌株多黏菌素耐药[39]。插入序列(*ISs*)或整合子可促进 *mcr* 的传播。研究表明，*ISApl1* 复合转座子在调动 *mcr-1* 的过程中起着关键的作用。*ISApl1* 属于 *IS30* 家族插入序列，通过两端反向重复序列形成典型复合转座子结构 *ISApl1-mcr-1-ISApl1*，其中 *mcr-1* 基因被两个 *ISApl1* 元件包围，这种结构使 *mcr-1* 可作为一个独立单元被整体转移。该转座子已被固定在 Inc*I2*、Inc*HI2* 和 Inc*X4* 等不同的质粒上[40] [41]。

3.2. 可移动遗传元件携带的外排泵基因

新型 RND 家族外排泵基因(如 *tmexCD-toprJ*)可通过质粒或转座子在菌株间水平转移。有研究报道，携带 *tmexCD-toprJ* 的肺炎克雷伯菌对替加环素和多黏菌素的 MIC 值分别上升 16 倍和 4 倍。此类基因还可与 *mcr* 基因共存，形成多重耐药表型[42]。这种多重耐药机制的出现，使得肺炎克雷伯菌对多种抗生素产生耐药性，进一步加剧了临床治疗的复杂性。

4. 细菌适应性耐药策略

4.1. 异质性耐药

异质性耐药指的是细菌群体中，存在对某种抗菌药物敏感性不同的亚群，通常表现为大部分亚群对某种抗菌药物敏感，而小部分亚群则表现出耐药性，这种现象是细菌耐药性进化过程中的一个中间阶段，可能导致常规药敏试验结果的可靠性降低，并最终引起临床治疗失败[43]。肺炎克雷伯菌的多黏菌素的异质性耐药已被广泛报道[44]，通常是与 PhoPQ 双组分调控系统、*pmrD* 基因的表达上调或 *mgrB* 基因失活有关。也有报道表示，介导 LPS 表达的 *lpxM* 基因、*yciM* 基因的突变导致异质性耐药[45]。一项对欧洲重症监护室分离的肺炎克雷伯菌菌株研究表明，插入序列对 *mgrB* 基因的破坏是肺炎克雷伯菌异质性耐药最常见的遗传修饰[46]。

4.2. 生物膜屏障效应

生物膜通过多糖基质(如荚膜多糖 CPS 和脂多糖 LPS)能够形成复杂的网络结构，限制多黏菌素等抗菌药物的渗透，阻碍药物与细菌细胞膜直接接触的同时降低药物有效浓度。处于生物膜中的细菌代谢活性降低，进入一种类似休眠的状态，导致“持留菌”形成[47]。持留菌的形成是细菌在面对抗菌压力时的一种生存策略，研究表明，持留菌通过降低代谢活性和增强抗氧化防御来抵御抗菌药物的杀伤[48]。生物膜内的细菌可以表达多种耐药基因，进一步增强其耐药性，研究表明，生物膜环境为细菌提供了对抗生素和金属的双重耐受性，可能利于 *mcr* 基因的稳定表达和传播[49]。

5. 小结

肺炎克雷伯菌对多黏菌素的耐药性已成为全球公共卫生领域的重大挑战。随着多黏菌素作为治疗多重耐药革兰阴性菌的最后防线被重新启用，其耐药机制的复杂性与传播速度远超预期。现有研究表明，耐药性主要由染色体突变和质粒介导的基因水平转移共同驱动，二者协同作用形成多重耐药表型，显著削弱了临床治疗效果。染色体介导的耐药机制聚焦于双组分调节系统(如 PhoPQ、PmrAB 和 CrrAB)的基因突变，通过脂多糖(LPS)修饰(如 L-Ara4N 和 pEtN 添加)。其中，*mgrB* 基因失活作为 PhoPQ 系统负调控的关键环节，在临床耐药株中高频出现，进一步揭示了基因突变对耐药表型的主导作用。

质粒介导的耐药机制则以 *mcr* 基因家族的传播为核心，尤其是 *mcr-1*、*mcr-8* 的全球流行，凸显了耐药基因通过可移动遗传元件跨界传播的威胁。此外，新兴亚型与碳青霉烯酶基因的共存，催生了“超级耐药”菌株，加剧了院内感染的控制难度。值得注意的是，荚膜多糖的过表达与生物膜形成通过物理屏障作用阻碍多黏菌素渗透，而外排泵基因的水平转移则为耐药性增添了新的维度。异质性耐药的存在更使得传统药敏试验的可靠性受到质疑，部分亚群在治疗压力下的存活可能成为耐药性扩散的潜在源头。

当前研究虽已阐明部分耐药机制，但仍存在显著空白。现有监测体系对新兴 *mcr* 亚型及复合耐药基因的识别能力有限，导致防控措施滞后于耐药性演变。未来研究需从多层面突破：首先，借助全基因组测序和实时纳米孔测序技术，解析其耐药基因谱，以此建立耐药基因的动态监测网络，预测高风险区域，实现早期预警；其次，开发针对 LPS 修饰通路或外排泵结构或功能的小分子抑制剂，解析磷酸乙醇胺转移酶活性中心，设计特异性小分子抑制剂，开发外排泵抑制剂，同时探索多黏菌素与 β-内酰胺类抗生素、噬菌体的联合治疗方案，开展多中心临床试验；最后，通过“One Health”策略统筹医疗、农业及环境管理，严格限制多黏菌素在养殖业的滥用，阻断耐药基因的跨界传播。唯有通过跨学科协作与技术创新，才能延缓耐药趋势，守护多黏菌素这一珍贵抗菌资源的临床价值。

参考文献

[1] Talbot, G.H., Bradley, J., Edwards, J.E., Gilbert, D., Scheld, M. and Bartlett, J.G. (2006) Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. *Clinical Infectious Diseases*, **42**, 657-668. https://doi.org/10.1086/499819

[2] Wyres, K.L. and Holt, K.E. (2018) *Klebsiella pneumoniae* as a Key Trafficker of Drug Resistance Genes from Environmental to Clinically Important Bacteria. *Current Opinion in Microbiology*, **45**, 131-139. https://doi.org/10.1016/j.mib.2018.04.004

[3] Clegg, S. and Murphy, C.N. (2016) Epidemiology and Virulence of *Klebsiella pneumoniae*. *Microbiology Spectrum*, **4**. https://doi.org/10.1128/microbiolspec.uti-0005-2012

[4] Martin, R.M. and Bachman, M.A. (2018) Colonization, Infection, and the Accessory Genome of *Klebsiella pneumoniae*. *Frontiers in Cellular and Infection Microbiology*, **8**, Article 4. https://doi.org/10.3389/fcimb.2018.00004

[5] Pu, D., Zhao, J., Chang, K., Zhuo, X. and Cao, B. (2023) “Superbugs” with Hypervirulence and Carbapenem Resistance in *Klebsiella pneumoniae*: The Rise of Such Emerging Nosocomial Pathogens in China. *Science Bulletin*, **68**, 2658-2670. https://doi.org/10.1016/j.scib.2023.09.040

[6] Nordmann, P., Cuzon, G. and Naas, T. (2009) The Real Threat of *Klebsiella pneumoniae* Carbapenemase-Producing Bacteria. *The Lancet Infectious Diseases*, **9**, 228-236. https://doi.org/10.1016/s1473-3099(09)70054-4

[7] Koch-Weser, J., Sidel, V.W., Federman, E.B., Kanarek, P., Finer, D.C. and Eaton, A.E. (1970) Adverse Effects of Sodium Colistimethate: Manifestations and Specific Reaction Rates During 317 Courses of Therapy. *Annals of Internal Medicine*, **72**, 857-868. https://doi.org/10.7326/0003-4819-72-6-857

[8] Kerob, D., Bouaziz, J.D., Sarfati, C., Pavie, J., Vignon-Pennamen, M.D., Menotti, J., *et al*. (2006) First Case of Cutaneous Reconstitution Inflammatory Syndrome Associated with HIV Infection and Leishmaniasis. *Clinical Infectious Diseases*, **43**, 664-666. https://doi.org/10.1086/506572

[9] Granata, G. and Petrosillo, N. (2017) Resistance to Colistin in *Klebsiella pneumoniae*: A 4.0 Strain? *Infectious Disease Reports*, **9**, Article 7104. https://doi.org/10.4081/idr.2017.7104

[10] Capone, A., Giannella, M., Fortini, D., Giordano, A., Meledandri, M., Ballardini, M., *et al*. (2013) High Rate of Colistin Resistance among Patients with Carbapenem-Resistant *Klebsiella pneumoniae* Infection Accounts for an Excess of Mortality. *Clinical Microbiology and Infection*, **19**, E23-E30. https://doi.org/10.1111/1469-0691.12070

[11] Liu, Y., Wang, Y., Walsh, T.R., Yi, L., Zhang, R., Spencer, J., *et al*. (2016) Emergence of Plasmid-Mediated Colistin Resistance Mechanism MCR-1 in Animals and Human Beings in China: A Microbiological and Molecular Biological Study. *The Lancet Infectious Diseases*, **16**, 161-168. https://doi.org/10.1016/s1473-3099(15)00424-7

[12] Velkov, T., Deris, Z.Z., Huang, J.X., Azad, M.A., Butler, M., Sivanesan, S., *et al*. (2013) Surface Changes and Polymyxin Interactions with a Resistant Strain of *Klebsiella pneumoniae*. *Innate Immunity*, **20**, 350-363. https://doi.org/10.1177/1753425913493337

[13] Li, L., Ma, J., Cheng, P., Li, M., Yu, Z., Song, X., *et al*. (2023) Roles of Two-Component Regulatory Systems in *Klebsiella pneumoniae*: Regulation of Virulence, Antibiotic Resistance, and Stress Responses. *Microbiological Research*, **272**, Article 127374. https://doi.org/10.1016/j.micres.2023.127374

[14] Groisman, E.A. (2016) Feedback Control of Two-Component Regulatory Systems. *Annual Review of Microbiology*, **70**, 103-124. https://doi.org/10.1146/annurev-micro-102215-095331

[15] Tierney, A.R. and Rather, P.N. (2019) Roles of Two-Component Regulatory Systems in Antibiotic Resistance. *Future Microbiology*, **14**, 533-552. https://doi.org/10.2217/fmb-2019-0002

[16] Elias, R., Duarte, A. and Perdigão, J. (2021) A Molecular Perspective on Colistin and *Klebsiella pneumoniae*: Mode of Action, Resistance Genetics, and Phenotypic Susceptibility. *Diagnostics*, **11**, Article 1165. https://doi.org/10.3390/diagnostics11071165

[17] Huang, J., Li, C., Song, J., Velkov, T., Wang, L., Zhu, Y., *et al*. (2020) Regulating Polymyxin Resistance in Gram-Negative Bacteria: Roles of Two-Component Systems PhoPQ and PmrAB. *Future Microbiology*, **15**, 445-459. https://doi.org/10.2217/fmb-2019-0322

[18] Shahab, M., Waqas, M., Fahira, A., Zhang, H., Zheng, G. and Huang, Z. (2024) Investigating the Role of PmRB Mutation on Colistin Antibiotics Drug Resistance in *Klebsiella pneumoniae*. *International Journal of Biological Macromolecules*, **281**, Article 136414. https://doi.org/10.1016/j.ijbiomac.2024.136414

[19] Jayol, A., Nordmann, P., Brink, A., Villegas, M., Dubois, V. and Poirel, L. (2017) High-Level Resistance to Colistin Mediated by Various Mutations in the *crrB* Gene among Carbapenemase-Producing *Klebsiella pneumoniae*. *Antimicrobial Agents and Chemotherapy*, **61**. https://doi.org/10.1128/aac.01423-17

[20] Cheng, Y., Lin, T., Lin, Y. and Wang, J. (2016) Amino Acid Substitutions of *CrrB* Responsible for Resistance to Colistin through *CrrC* in *Klebsiella pneumoniae*. *Antimicrobial Agents and Chemotherapy*, **60**, 3709-3716. https://doi.org/10.1128/aac.00009-16

[21] McConville, T.H., Annavajhala, M.K., Giddins, M.J., Macesic, N., Herrera, C.M., Rozenberg, F.D., *et al*. (2020) *CrrB* Positively Regulates High-Level Polymyxin Resistance and Virulence in *Klebsiella pneumoniae*. *Cell Reports*, **33**, Article 108313. https://doi.org/10.1016/j.celrep.2020.108313

[22] Kim, S.J., Shin, J.H., Kim, H. and Ko, K.S. (2024) Roles of *CrrAB* Two-Component Regulatory System in *Klebsiella pneumoniae*: Growth Yield, Survival in Initial Colistin Treatment Stage, and Virulence. *International Journal of Antimicrobial Agents*, **63**, Article 107011. https://doi.org/10.1016/j.ijantimicag.2023.107011

[23] Cheng, Y., Lin, T., Lin, Y. and Wang, J. (2018) A Putative RND-Type Efflux Pump, H239_3064, Contributes to Colistin Resistance through *CrrB* in *Klebsiella pneumoniae*. *Journal of Antimicrobial Chemotherapy*, **73**, 1509-1516. https://doi.org/10.1093/jac/dky054

[24] Poirel, L., Jayol, A., Bontron, S., Villegas, M.-V., Ozdamar, M., Turkoglu, S., *et al*. (2014) The *mgrB* Gene as a Key Target for Acquired Resistance to Colistin in *Klebsiella pneumoniae*. *Journal of Antimicrobial Chemotherapy*, **70**, 75-80. https://doi.org/10.1093/jac/dku323

[25] Bray, A.S., Smith, R.D., Hudson, A.W., Hernandez, G.E., Young, T.M., George, H.E., *et al*. (2022) *MgrB*-Dependent Colistin Resistance in *Klebsiella pneumoniae* Is Associated with an Increase in Host-To-Host Transmission. *mBio*, **13**,

e03595-21. https://doi.org/10.1128/mbio.03595-21

[26] Lippa, A.M. and Goulian, M. (2009) Feedback Inhibition in the PhOQ/PhOP Signaling System by a Membrane Peptide. *PLOS Genetics*, **5**, e1000788. https://doi.org/10.1371/journal.pgen.1000788

[27] Liu, X., Wu, Y., Zhu, Y., Jia, P., Li, X., Jia, X., *et al*. (2022) Emergence of Colistin-Resistant Hypervirulent *Klebsiella pneumoniae* (CoR-HvKp) in China. *Emerging Microbes & Infections*, **11**, 648-661. https://doi.org/10.1080/22221751.2022.2036078

[28] Cannatelli, A., D'Andrea, M.M., Giani, T., Di Pilato, V., Arena, F., Ambretti, S., *et al*. (2013) *In Vivo* Emergence of Colistin Resistance in *Klebsiella pneumoniae* Producing Kpc-Type Carbapenemases Mediated by Insertional Inactivation of the PhOQ/PhOP *mgrB* Regulator. *Antimicrobial Agents and Chemotherapy*, **57**, 5521-5526. https://doi.org/10.1128/aac.01480-13

[29] Cannatelli, A., Giani, T., D'Andrea, M.M., Di Pilato, V., Arena, F., Conte, V., *et al*. (2014) *MgrB* Inactivation Is a Common Mechanism of Colistin Resistance in Kpc-Producing *Klebsiella pneumoniae* of Clinical Origin. *Antimicrobial Agents and Chemotherapy*, **58**, 5696-5703. https://doi.org/10.1128/aac.03110-14

[30] Talat, A., Khan, F. and Khan, A.U. (2024) Genome Analyses of Colistin-Resistant High-Risk *bla*$_{NDM-5}$ Producing *Klebsiella pneumoniae* ST147 and Pseudomonas Aeruginosa ST235 and ST357 in Clinical Settings. *BMC Microbiology*, **24**, Article No. 174. https://doi.org/10.1186/s12866-024-03306-4

[31] Olaitan, A.O., Morand, S. and Rolain, J. (2014) Mechanisms of Polymyxin Resistance: Acquired and Intrinsic Resistance in Bacteria. *Frontiers in Microbiology*, **5**, Article 643. https://doi.org/10.3389/fmicb.2014.00643

[32] Maharramov, E., Czikkely, M.S., Szili, P., Farkas, Z., Grézal, G., Daruka, L., *et al*. (2025) Exploring the Principles behind Antibiotics with Limited Resistance. *Nature Communications*, **16**, Article No. 1842. https://doi.org/10.1038/s41467-025-56934-3

[33] Xu, L., Li, J., Wu, W., Wu, X. and Ren, J. (2024) *Klebsiella pneumoniae* Capsular Polysaccharide: Mechanism in Regulation of Synthesis, Virulence, and Pathogenicity. *Virulence*, **15**, Article 2439509. https://doi.org/10.1080/21505594.2024.2439509

[34] Neumann, B., Stürhof, C., Rath, A., Kieninger, B., Eger, E., Müller, J.U., *et al*. (2023) Detection and Characterization of Putative Hypervirulent *Klebsiella pneumoniae* Isolates in Microbiological Diagnostics. *Scientific Reports*, **13**, Article No. 19025. https://doi.org/10.1038/s41598-023-46221-w

[35] Llobet, E., Campos, M.A., Giménez, P., Moranta, D. and Bengoechea, J.A. (2011) Analysis of the Networks Controlling the Antimicrobial-Peptide-Dependent Induction of *Klebsiella pneumoniae* Virulence Factors. *Infection and Immunity*, **79**, 3718-3732. https://doi.org/10.1128/iai.05226-11

[36] Ling, Z., Yin, W., Shen, Z., Wang, Y., Shen, J. and Walsh, T.R. (2020) Epidemiology of Mobile Colistin Resistance Genes *mcr*-1 to *mcr*-9. *Journal of Antimicrobial Chemotherapy*, **75**, 3087-3095. https://doi.org/10.1093/jac/dkaa205

[37] Liu, M.C., Jian, Z., Liu, W., Li, J. and Pei, N. (2022) One Health Analysis of *mcr*-Carrying Plasmids and Emergence of *mcr-10.1* in Three Species of Klebsiella Recovered from Humans in China. *Microbiology Spectrum*, **10**, e02306-22. https://doi.org/10.1128/spectrum.02306-22

[38] Chen, F., Lauderdale, T., Huang, W., Shiau, Y., Wang, H. and Kuo, S. (2021) Emergence of *mcr*-1, *mcr*-3 and *mcr*-8 in Clinical *Klebsiella pneumoniae* Isolates in Taiwan. *Clinical Microbiology and Infection*, **27**, 305-307. https://doi.org/10.1016/j.cmi.2020.07.043

[39] El-Sayed Ahmed, M.A.E., Zhong, L., Shen, C., Yang, Y., Doi, Y. and Tian, G. (2020) Colistin and Its Role in the Era of Antibiotic Resistance: An Extended Review (2000-2019). *Emerging Microbes & Infections*, **9**, 868-885. https://doi.org/10.1080/22221751.2020.1754133

[40] Snesrud, E., He, S., Chandler, M., Dekker, J.P., Hickman, A.B., McGann, P., *et al*. (2016) A Model for Transposition of the Colistin Resistance Gene *mcr-1* by IS*apl1*. *Antimicrobial Agents and Chemotherapy*, **60**, 6973-6976. https://doi.org/10.1128/aac.01457-16

[41] Snesrud, E., McGann, P. and Chandler, M. (2018) The Birth and Demise of the IS *apl1-mcr-1*-IS*apl1* Composite Transposon: The Vehicle for Transferable Colistin Resistance. *mBio*, **9**. https://doi.org/10.1128/mbio.02381-17

[42] Liu, C., Guo, J., Lu, M., Shen, N. and Du, P. (2023) Dissemination of the Mobilised RND Efflux Pump Gene Cluster *tmexCD-toprJ* among *Klebsiella pneumoniae*. *The Lancet Microbe*, **4**, e135. https://doi.org/10.1016/s2666-5247(22)00325-1

[43] Stojowska-Swędrzyńska, K., Łupkowska, A., Kuczyńska-Wiśnik, D. and Laskowska, E. (2021) Antibiotic Heteroresistance in *Klebsiella pneumoniae*. *International Journal of Molecular Sciences*, **23**, 449. https://doi.org/10.3390/ijms23010449

[44] Wang, Y., Ma, X., Zhao, L., He, Y., Yu, W., Fu, S., *et al*. (2022) Heteroresistance Is Associated with *in Vitro* Regrowth during Colistin Treatment in Carbapenem-Resistant *Klebsiella pneumoniae*. *Frontiers in Microbiology*, **13**, Article 868991. https://doi.org/10.3389/fmicb.2022.868991

[45] Halaby, T., Kucukkose, E., Janssen, A.B., Rogers, M.R.C., Doorduijn, D.J., van der Zanden, A.G.M., *et al*. (2016) Genomic Characterization of Colistin Heteroresistance in *Klebsiella pneumoniae* during a Nosocomial Outbreak. *Antimicrobial Agents and Chemotherapy*, **60**, 6837-6843. https://doi.org/10.1128/aac.01344-16

[46] Braspenning, A.J.M.M., Rajakani, S.G., Sey, A., El Bounja, M., Lammens, C., Glupczynski, Y., *et al*. (2024) Assessment of Colistin Heteroresistance among Multidrug-Resistant *Klebsiella pneumoniae* Isolated from Intensive Care Patients in Europe. *Antibiotics*, **13**, Article 281. https://doi.org/10.3390/antibiotics13030281

[47] Vatansever, C., Ozer, B., Atac, N., Guler, O.U., Kilicoglu, B.K., Berkkan, M., *et al*. (2022) Efficacy of Amikacin and Meropenem on Colistin-Induced *Klebsiella pneumoniae* Persisters. *Microbial Drug Resistance*, **28**, 765-772. https://doi.org/10.1089/mdr.2021.0207

[48] Abokhalil, R.N., Elkhatib, W.F., Aboulwafa, M.M. and Hassouna, N.A. (2020) Persisters of *Klebsiella pneumoniae* and Proteus Mirabilis: A Common Phenomenon and Different Behavior Profiles. *Current Microbiology*, **77**, 1233-1244. https://doi.org/10.1007/s00284-020-01926-3

[49] Mondol, S.M., Hossain, M.A. and Haque, F.K.M. (2025) Comprehensive Genomic Insights into a Highly Pathogenic Clone ST656 of *mcr*8.1 Containing Multidrug-Resistant *Klebsiella pneumoniae* from Bangladesh. *Scientific Reports*, **15**, Article No. 5909. https://doi.org/10.1038/s41598-025-90414-4