

多黏菌素在耐药鲍曼不动杆菌血流感染中的应用进展

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【摘要】 近年来革兰阴性杆菌血流感染率呈持续增加趋势, 其中耐药菌所致感染病死率更高、住院时间更长, 尤其是耐碳青霉烯类鲍曼不动杆菌 (CRAB) 血流感染。多黏菌素于 20 世纪 50 年代开始用于临床, 具有对多重耐药和广泛耐药革兰阴性杆菌抗菌活性, 也可作为革兰阴性杆菌细胞包膜的有效通透剂。多黏菌素保留应用于微生物学明确的耐药革兰阴性杆菌感染, 世界卫生组织将其分类为对人类感染具有重要临床意义的抗菌药物, 可以用于治疗耐药鲍曼不动杆菌感染。本文对多黏菌素治疗耐药鲍曼不动杆菌血流感染的临床治疗进行综述, 以期对临床医生用药提供参考。

【关键词】 多黏菌素; 耐碳青霉烯类鲍曼不动杆菌; 血流感染; 多重耐药; 泛耐药

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Application progress of polymyxin in bloodstream infection of drug-resistant *Acinetobacter baumannii*

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【Abstract】 In recent years, the bloodstream infection rate of Gram-negative bacilli has continued to increase. Among them, drug-resistant bacteria have a higher mortality rate and longer hospital stay, especially the bloodstream infection of carbapenem-resistant *Acinetobacter baumannii* (CRAB). Polymyxin began to be used clinically in the 1950s and has antibacterial activity against multidrug resistant and poly drug-resistant Gram-negative bacilli. It can also be used as an effective permeation agent for the cell envelope of Gram-negative bacilli. Polymyxin is reserved for microbiologically clear drug-resistant Gram-negative bacilli infections. The World Health Organization classifies polymyxin as an antimicrobial drug with clinical significance for human infections and can be used to treat drug-resistant *Acinetobacter baumannii* infection. This article reviews the clinical treatment of polymyxin in bloodstream infections of drug-resistant *Acinetobacter baumannii*, to provide reference for clinical medication.

【Key words】 Polymyxin; Carbapenem-resistant *Acinetobacter baumannii*; Bloodstream infection; Multidrug resistant; Extensively drug resistant

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耐药革兰阴性杆菌是院内血流感染的主要病原菌, 近年来感染率呈持续增加趋势^[1], 所致感染比敏感菌病死率更高、住院时间更长^[2], 临床预后差、治疗困难, 带来了沉重的社会负担。伴随着重症医学专业的发展, 部分免疫力低下的患者或伴有基础疾病的患者成为血流感染的重点人群, 侵入性操作或治疗也增加了患者血流感染的机会。耐药革兰阴性杆菌的治疗药物选择有限, 其中多黏菌素于 20 世纪 50 年代用于临床, 作用机制包括破坏革兰阴性杆菌外膜完整性、快速杀菌、与脂多糖结合及提高其他抗菌药物活性等^[3], 对多重耐药 (multidrug resistant, MDR) 和广泛耐药 (extensively drug resistant, XDR) 革兰阴性杆菌有抗菌活性, 也可作为革兰阴性杆菌细胞包膜有效通透剂^[4], 用于临床重症感染的治疗。现就多黏菌素治疗 MDR 和 XDR 鲍曼不动杆菌尤其是耐碳青霉烯类鲍曼不动杆菌 (carbapenem-resistant *Acinetobacter baumannii*, CRAB) 血流感染的临床现状综述如下。

1 耐药鲍曼不动杆菌血流感染现状

耐药菌感染给临床治疗带来巨大威胁, 尤其是 CRAB 感染^[5], 抗菌药物选择有限, 新抗菌药物疗效还不确定^[6]。抗菌药物单用效果不佳, 而联合治疗同样给临床带来新的困境, 在改善预后的同时, 也可能会带来更严重的耐药性。鲍曼不动杆菌血流感染相对其他革兰阴性杆菌引起的炎症指标升高并没有那么明显^[7], 但临床可以观察到高热或伴随快速进展的脓毒性休克。更为严峻的是, 45 个国家 / 地区 200 多个医疗中心连续监测 20 年收集 264 901 例血流感染患者的临床数据和分离菌株显示, MDR 肠杆菌感染率从 1997 年的 6.2% 增加到 2016 年的 15.8%, 血流感染发生率持续增加, 作为非发酵菌的鲍曼不动杆菌多重耐药率最高, 而多黏菌素是唯一对耐药不动杆菌属复合物敏感的抗菌药物^[8]。国内耐药菌形势更为严峻, 2018 年中国细菌耐药监测网 (China Antimicrobial Surveillance Network, CHINET) 结果显示, 鲍曼不动杆菌对亚胺培南和美罗培南的耐药率快速升

高至 56.1%，全国地区差异性较大，部分地区检出率居高不下^[9]。2019 年 CHINET 结果显示，鲍曼不动杆菌对亚胺培南和美罗培南的耐药率升高至 77.7%、79.0%；有地区鲍曼不动杆菌对碳青霉烯类耐药率高达 80.1%~80.5%^[10]。鲍曼不动杆菌对大多数抗菌药物耐药性较高，除多黏菌素 B 和米诺环素外，对其他抗菌药物的耐药率在 59.4%~87.7%^[11]。预后方面，国外一项回顾性研究显示，鲍曼不动杆菌血流感染患者的病死率高达 58%^[12]。

2 多黏菌素

2.1 多黏菌素临床应用现状：临床主要有多黏菌素 B 和多黏菌素 E，后者也称黏菌素。国内静脉制剂为多黏菌素 B，欧洲及大洋洲多为多黏菌素 E，美洲及东南亚地区有两种剂型。多黏菌素联合其他抗菌药物治疗耐碳青霉烯类革兰阴性杆菌 (carbapenem-resistant organism, CRO) 感染的疗效与感染部位和致病菌有关，治疗中枢感染可以同时给予鞘内注射，而肺部耐药菌感染可联合雾化吸入治疗^[13-14]。研究证实，多黏菌素有益于改善耐革兰阴性杆菌感染的临床疗效，保留应用于微生物学明确的 XDR 革兰阴性杆菌感染^[15]。世界卫生组织将多黏菌素分类为对人类感染具有重要临床意义的抗菌药物^[16]。由于耐药菌感染形势严峻，多黏菌素已成为治疗耐革兰阴性杆菌感染的主要治疗选择之一^[17]。为方便描述，本文统一使用多黏菌素代替多黏菌素类药物。

2.2 多黏菌素的分子结构与药物特点：多黏菌素 B 与多黏菌素 E 的体外抗菌活性接近，多黏菌素 B 以其活性体 (硫酸多黏菌素 B) 直接给药，多黏菌素 E 以无活性前体黏菌素甲磺酸盐 (colistin methanesulfonate, CMS) 或硫酸黏菌素给药，二者肾毒性发生率在 7.1%~40.5%^[18]，部分停药后可恢复。多黏菌素日剂量大于 150 mg 是多黏菌素相关急性肾损伤的独立危险因素，严重低蛋白血症和使用大剂量血管活性药物的患者急性肾损伤发生率更高^[19]。

2.3 多黏菌素应用剂量：多黏菌素 B 负荷剂量 2.0~2.5 mg/kg (20~25 kU/kg)；12~24 h 后维持剂量 2.5~3.0 mg·kg⁻¹·d⁻¹，分 2 次给药，建议持续静脉输注时间大于 1 h^[20]。多黏菌素 E 以黏菌素活性基质 (colistin base activity, CBA) 计算剂量，负荷剂量为 5 mg/kg CBA (CMS 150 kU/kg)，最大剂量不超过 300 mg CBA/9 000 kU CMS，持续静脉输注 0.5~1.0 h；12~24 h 后每天给予维持剂量 300~360 mg CBA/9 000~10 900 kU CMS，分 2 次给药^[14]，根据肾功能调整每日给药剂量。

3 多黏菌素治疗耐药鲍曼不动杆菌血流感染

3.1 多黏菌素单药治疗：国外一项多中心随机对照研究对比了多黏菌素 (多黏菌素 E) 单药与联合大剂量美罗培南治疗 CRO 感染的疗效，结果显示，多黏菌素单药治疗组与联合治疗组 14 d 临床失败率差异无统计学意义 (79% 比 73%)；次要结局 14 d 总病死率 (32% 比 34%)、28 d 病死率 (43% 比 45%) 差异也无统计学意义，多黏菌素联合美罗培南联合方案可能无法改善严重鲍曼不动杆菌感染患者的预后；但亚组分析显示，联合治疗组对机械通气的危重患者更有帮助，可缩短撤机时间，因此，多黏菌素单药与联合治疗对比有

待更深入的研究进行评估^[21]。

一项涉及 118 例 CRAB 血流感染患者的观察性队列研究 (包含源于肺部感染的 76 例血流感染和 18 例原发血流感染) 显示，多黏菌素单药治疗组病死率为 55.3% (42/76)，多黏菌素联合替加环素治疗组病死率为 57.1% (24/42)，即便大剂量多黏菌素与替加环素联合治疗也未见到患者总病死率降低，这种联合方案可能无法改善 CRAB 血流感染患者预后，乐观的是，经验性应用多黏菌素与 30 d 总病死率相关^[22]。

一项涉及 MDR/XDR 鲍曼不动杆菌血流感染的多中心回顾性研究纳入了 107 例患者，主要观察终点为 14 d 病死率，次要终点为微生物根除率和临床改善情况。其中 36 例 XDR 鲍曼不动杆菌血流感染患者采用多黏菌素单药治疗，71 例 MDR 鲍曼不动杆菌血流感染患者采用非多黏菌素联合治疗 (联合方案主要包括：头孢哌酮舒巴坦联合氨基糖苷、碳青霉烯联合氨基糖苷、替加环素联合氨基糖苷、碳青霉烯联合舒巴坦、替加环素联合头孢哌酮舒巴坦等)，结果显示，两种方案的临床治疗成功率差异无统计学意义 (77.1% 比 77.2%， $P=0.45$)，推测可能与研究入组患者病原菌耐药情况不同有关^[23]。上述有关多黏菌素单药治疗耐药鲍曼不动杆菌血流感染的对比性观察中，多数研究为回顾性研究，主要对单药治疗与两种抗菌药物联合治疗的疗效观察，未见明确的临床有效性差别。

3.2 多黏菌素为基础的联合治疗：因 CRAB 血流感染病死率高，临床上采用多种抗菌药物联合治疗来改善预后。体外药敏试验显示，对替加环素耐药鲍曼不动杆菌联合治疗有效，多黏菌素联合左氧氟沙星、丁胺卡那霉素或亚胺培南都具有体外协同活性^[24]。

多黏菌素为基础的联合治疗方案较多，有研究显示，多黏菌素联合利福平虽不能降低 XDR 鲍曼不动杆菌感染 30 d 病死率，但微生物根除率显著增加^[25]。多黏菌素联合利福平治疗 29 例 CRAB 感染患者 (10 例血流感染、17 例肺部感染、合并肺炎和血流感染 2 例) 的研究显示，联合治疗有临床疗效，并具备临床安全性^[26]。多黏菌素联合磷霉素治疗 CRAB 感染的一项前瞻性研究显示，联合治疗组比多黏菌素单药治疗组患者微生物学应答显著改善，临床预后更好，可降低病死率^[27]。

多黏菌素与糖肽类药物联合治疗 CRAB 感染的相关研究显示，联合治疗临床治愈率虽未见明显提升，但联合治疗疗程大于 5 d 是改善预后的独立相关因素^[28]。达托霉素联合小剂量多黏菌素治疗 CRAB 也有活性，当多黏菌素达到对鲍曼不动杆菌菌株最低抑制浓度时，达托霉素活性显著增加^[29]。目前多黏菌素与糖肽类抗菌药物联合用药仅见于上述文献，国内鲜见报道，临床上有个别患者存在二者联用的情况，但出发点基于广覆盖病原微生物，考虑到两种药物的肾毒性，临床应用应慎重。上述联合治疗方案的出发点多从药物作用机制方面考虑，相比单药治疗可以观察到临床疗效一定程度的改善，而且所联合药物的体外药敏有协同作用。而部分体外耐药的抗菌药物也可以联合应用，多黏菌素联合

体外药敏结果耐药的抗菌药物在临床治疗中也观察到疗效,常见的为多黏菌素与碳青霉烯类抗菌药物的联合治疗。一项涉及9例CRAB血流感染患者的小样本研究显示,多黏菌素联合体外耐药抗菌药物治疗方案组病死率明显低于多黏菌素单药治疗组^[30]。这些小样本临床研究也为临床医生提供了治疗参考。限于研究数量、样本量,联合方案的临床疗效还有待研究进一步证实。

联合方案中多黏菌素联合替加环素、舒巴坦或碳青霉烯类药物更为常见。因耐药机制不同,体外药敏也有区别,抗菌药物的联合方案较多,难以从前瞻性研究中特殊设定固定的联合治疗方案。MDR/XDR 鲍曼不动杆菌血流感染治疗的荟萃分析(共纳入29项研究、涉及2529例患者)显示,相比两种抗菌药物的联合治疗,多黏菌素、舒巴坦和替加环素三药联合方案的临床治愈率最高;而与多黏菌素单药治疗或多黏菌素联合替加环素治疗相比,多黏菌素联合舒巴坦的微生物治愈率更高^[31]。

多数研究支持耐药鲍曼不动杆菌血流感染采用多黏菌素为基础的联合治疗,但联合治疗方案依然充满挑战。相比多黏菌素单药治疗,多黏菌素联合治疗方案中对联合药物的选择,以及联合抗菌药物的种类都有待于更多临床数据进行观察分析。CRO血流感染明确前48h内多黏菌素联合治疗可提高微生物清除率、降低病死率^[32],因此,如何根据临床证据把握抗菌药物使用时机、如何制定联合方案,可能会成为临床耐药菌血流感染关注的热点。

4 多黏菌素耐药性

随着临床多黏菌素使用增加,多黏菌素耐药数据报告逐渐增多,研究显示,多黏菌素单药治疗和联合治疗28d多黏菌素耐药检出率分别为6%(11/198)、5%(10/208),虽然差异无统计学意义,但耐药菌特别是多黏菌素耐药菌血流感染可能面临更严峻挑战^[21]。匈牙利一项研究显示,血培养分离株中不动杆菌属多黏菌素耐药率为2.6%^[33]。多黏菌素耐药性增加会给临床治疗带来难以估量的影响,土耳其一项回顾性研究多变量分析显示,碳青霉烯[优势比(odds ratio, OR)=1.02, 95%可信区间(95% confidence interval, 95%CI)为1.01~1.04, P=0.002]和多黏菌素(OR=1.1, 95%CI为1.03~1.17, P=0.001)的最低抑菌浓度(minimum inhibitory concentration, MIC)都与病死率显著相关,其中鲍曼不动杆菌多黏菌素耐药率为2.1%^[12],该作者先前研究结果为6%^[34],耐药率增加会导致治疗难度更高。但多黏菌素耐药鲍曼不动杆菌的治疗仍存在争议,多黏菌素是否可以继续用于治疗多黏菌素耐药革兰阴性杆菌感染仍有待进一步研究评估。

5 小结

耐药鲍曼不动杆菌血流感染患者病死率高,临床治疗困难,多黏菌素、舒巴坦和替加环素有良好的体外活性,都可以用于这类患者的治疗^[35]。虽然有研究显示,多黏菌素无法降低鲍曼不动杆菌血流感染病死率^[36],但多项回顾性观察研究支持多黏菌素联合治疗方案,血流感染患者联合治疗与生存率存在显著关联,28d全因病死率更低^[37-40]。多

黏菌素联合碳青霉烯的方案也许优于多黏菌素联合替加环素,除多黏菌素联合碳青霉烯类药物、替加环素及舒巴坦外,临床也可以根据药敏联合丁胺卡那霉素、利福平或磷霉素,甚至可以观察联合糖肽类抗菌药物的体外协同作用或临床疗效。3种及以上抗菌药物联合治疗有更高的临床治愈率^[31],对明确血流感染的脓毒性休克患者也不失为一种更好的治疗选择。另外,与碳青霉烯敏感鲍曼不动杆菌血流感染患者相比,CRAB所致血流感染临床结局更差,更容易出现抗微生物治疗延迟(delay in the initiation of appropriate antimicrobial therapy, DAAT),而DAAT是不良预后独立的预测因子^[41],因此,耐药鲍曼不动杆菌血流感染治疗,应早期应用有效抗菌药物、联合治疗特别是以多黏菌素为基础的联合治疗可以改善患者预后,也有待更多的前瞻性的大样本观察性研究提供循证医学证据。

一项多中心开放随机对照试验比较了单用多黏菌素与多黏菌素联合美罗培南治疗CRO引起的严重感染,研究结果也许可以为耐药菌治疗提供帮助^[42];早期研究结果显示,联合治疗可以缩短呼吸机支持时间,特别是对于严重CRAB血流感染患者^[43],联合治疗的临床疗效值得期待并需进一步研究。国内医疗机构也在开展对耐药革兰阴性杆菌血流感染治疗的前瞻性随机对照研究,期待未来可以看到更多相关循证医学证据。

利益冲突 所有作者均声明不存在利益冲突

参考文献

- [1] Itokazu GS, Quinn JP, Bell-Dixon C, et al. Antimicrobial resistance rates among aerobic Gram-negative bacilli recovered from patients in intensive care units: evaluation of a national postmarketing surveillance program [J]. Clin Infect Dis, 1996, 23 (4): 779-784. DOI: 10.1093/clinids/23.4.779.
- [2] Blot S, Vandewoude K, De Bacquer D, et al. Nosocomial bacteremia caused by antibiotic-resistant Gram-negative bacteria in critically ill patients: clinical outcome and length of hospitalization [J]. Clin Infect Dis, 2002, 34 (12): 1600-1606. DOI: 10.1086/340616.
- [3] Nation RL, Li J, Turnidge JD. The urgent need for clear and accurate information on the polymyxins [J]. Clin Infect Dis, 2013, 57 (11): 1656-1657. DOI: 10.1093/cid/cit522.
- [4] Bergen PJ, Landersdorfer CB, Lee HJ, et al. 'Old' antibiotics for emerging multidrug-resistant bacteria [J]. Curr Opin Infect Dis, 2012, 25 (6): 626-633. DOI: 10.1097/QCO.0b013e328358afe5.
- [5] Willyard C. The drug-resistant bacteria that pose the greatest health threats [J]. Nature, 2017, 543 (7643): 15. DOI: 10.1038/nature.2017.21550.
- [6] Peri AM, Doi Y, Potoski BA, et al. Antimicrobial treatment challenges in the era of carbapenem resistance [J]. Diagn Microbiol Infect Dis, 2019, 94 (4): 413-425. DOI: 10.1016/j.diagmicrobio.2019.01.020.
- [7] 高星儿. 老年恶性血液病化疗患者合并血流感染的临床研究 [J]. 中国中西医结合急救杂志, 2018, 25 (1): 72-75. DOI: 10.3969/j.issn.1008-9691.2018.01.018. Gao XE. A clinical study of elderly chemotherapy patients with malignant hematopathy combined with blood stream infection [J]. Chin J TCM WM Crit Care, 2018, 25 (1): 72-75. DOI: 10.3969/j.issn.1008-9691.2018.01.018.
- [8] Diekema DJ, Hsueh PR, Mendes RE, et al. The microbiology of bloodstream infection: 20-year trends from the SENTRY Antimicrobial Surveillance Program [J]. Antimicrob Agents Chemother, 2019, 63 (7): e00355-19. DOI: 10.1128/AAC.00355-19.
- [9] 胡付品, 郭燕, 朱德妹, 等. 2018年CHINET中国细菌耐药性监测 [J]. 中国感染与化疗杂志, 2020, 20 (1): 1-10. DOI: 10.16718/j.1009-7708.2020.01.001. Hu FP, Guo Y, Zhu DM, et al. CHINET surveillance of bacterial resistance in China: 2018 report [J]. Chin J Infect Chemother, 2020, 20 (1): 1-10. DOI: 10.16718/j.1009-7708.2020.01.001.
- [10] 胡付品, 郭燕, 朱德妹, 等. 2019年CHINET三级医院细菌耐药性监测 [J]. 中国感染与化疗杂志, 2020, 20 (3): 233-243. DOI: 10.16718/j.1009-7708.2020.03.001. Hu FP, Guo Y, Zhu DM, et al. CHINET surveillance of bacterial

- resistance across tertiary hospitals in 2019 [J]. *Chin J Infect Chemother*, 2020, 20 (3): 233–243. DOI: 10.16718/j.1009-7708.2020.03.001.
- [11] 徐慧, 徐岷, 刘彩林, 等. 2014~2019 年郑州大学第一附属医院血培养分离病原菌临床分布及耐药性分析 [J]. *现代检验医学杂志*, 2021, 36 (1): 136–140. DOI: 10.3969/j.issn.1671-7414.2021.01.034.
- Xu H, Xu M, Liu CL, et al. Clinical distribution and antibiotic resistance of the blood culture isolates from the First Affiliated Hospital of Zhengzhou University, 2014–2019 [J]. *J Mod Lab Med*, 2021, 36 (1): 136–140. DOI: 10.3969/j.issn.1671-7414.2021.01.034.
- [12] Aydın M, Ergönül Ö, Azap A, et al. Rapid emergence of colistin resistance and its impact on fatality among healthcare-associated infections [J]. *J Hosp Infect*, 2018, 98 (3): 260–263. DOI: 10.1016/j.jhin.2017.11.014.
- [13] 中国研究型医院学会危重医学专业委员会, 中国研究型医院学会感染性疾病循证与转化专业委员会. 多黏菌素临床应用中国专家共识 [J]. *中华危重病急救医学*, 2019, 31 (10): 1194–1198. DOI: 10.3760/cma.j.issn.2095-4352.2019.10.003.
- Chinese Research Hospital Association of Critical Care Medicine, Chinese Research Hospital Association of Evidence base and Translational Infectious Diseases. Chinese expert consensus on polymyxins in the clinical practice [J]. *Chin Crit Care Med*, 2019, 31 (10): 1194–1198. DOI: 10.3760/cma.j.issn.2095-4352.2019.10.003.
- [14] Tsuji BT, Pogue JM, Zavascki AP, et al. International consensus guidelines for the optimal use of the polymyxins: endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Antimicrobial Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP) [J]. *Pharmacotherapy*, 2019, 39 (1): 10–39. DOI: 10.1002/phar.2209.
- [15] Katz DE, Marchaim D, Assous MV, et al. Ten years with colistin: a retrospective case series [J]. *Int J Clin Pract*, 2016, 70 (9): 706–711. DOI: 10.1111/ijcp.12830.
- [16] Collignon PJ, Conly JM, Andremont A, et al. World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies to control antimicrobial resistance from food animal production [J]. *Clin Infect Dis*, 2016, 63 (8): 1087–1093. DOI: 10.1093/cid/ciw475.
- [17] 赵双平, 闫莉婷, 王池香, 等. 以多黏菌素 B 为基础联合治疗 ICU 泛耐药革兰阴性菌感染脓毒症的临床分析 [J]. *中华危重病急救医学*, 2020, 32 (2): 150–154. DOI: 10.3760/cma.j.cn121430-20200108-00028.
- Zhao SP, Yan LT, Wang CX, et al. Clinical analysis of sepsis with extensively drug resistant Gram-negative bacteria in intensive care unit treated with polymyxin B-based combination therapy [J]. *Chin Crit Care Med*, 2020, 32 (2): 150–154. DOI: 10.3760/cma.j.cn121430-20200108-00028.
- [18] Mattos KPH, Gouvêa IR, Quintanilha JCF, et al. Polymyxin B clinical outcomes: a prospective study of patients undergoing intravenous treatment [J]. *J Clin Pharm Ther*, 2019, 44 (3): 415–419. DOI: 10.1111/jcpt.12801.
- [19] 王妍, 陈显成, 郭晓芳, 等. ICU 重症感染患者发生多黏菌素 B 相关性急性肾损伤的影响因素分析 [J]. *中华危重病急救医学*, 2020, 32 (6): 716–720. DOI: 10.3760/cma.j.cn121430-20200304-00207.
- Wang Y, Chen XC, Guo XF, et al. Analysis of risk factors of polymyxin B-associated acute kidney injury in intensive care unit patients with severe infection [J]. *Chin Crit Care Med*, 2020, 32 (6): 716–720. DOI: 10.3760/cma.j.cn121430-20200304-00207.
- [20] Sandri AM, Landersdorfer CB, Jacob J, et al. Pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis [J]. *J Antimicrob Chemother*, 2013, 68 (3): 674–677. DOI: 10.1093/jac/dks437.
- [21] Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial [J]. *Lancet Infect Dis*, 2018, 18 (4): 391–400. DOI: 10.1016/S1473-3099(18)30099-9.
- [22] Amat T, Gutiérrez-Pizarraya A, Machuca I, et al. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant *Acinetobacter baumannii* [J]. *Clin Microbiol Infect*, 2018, 24 (6): 630–634. DOI: 10.1016/j.cmi.2017.09.016.
- [23] Balkan H, Batirel A, Karabay O, et al. Comparison of colistin monotherapy and non-colistin combinations in the treatment of multi-drug resistant *Acinetobacter spp.* bloodstream infections: a multicenter retrospective analysis [J]. *Indian J Pharmacol*, 2015, 47 (1): 95–100. DOI: 10.4103/0253-7613.150383.
- [24] Principe L, D'Arezzo S, Capone A, et al. *In vitro* activity of tigecycline in combination with various antimicrobials against multidrug resistant *Acinetobacter baumannii* [J]. *Ann Clin Microbiol Antimicrob*, 2009, 8: 18. DOI: 10.1186/1476-0711-8-18.
- [25] Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial [J]. *Clin Infect Dis*, 2013, 57 (3): 349–358. DOI: 10.1093/cid/cit253.
- [26] Bassetti M, Repetto E, Righi E, et al. Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections [J]. *J Antimicrob Chemother*, 2008, 61 (2): 417–420. DOI: 10.1093/jac/dkm509.
- [27] Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomicin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections [J]. *Antimicrob Agents Chemother*, 2014, 58 (9): 5598–5601. DOI: 10.1128/AAC.02435-13.
- [28] Petrosillo N, Giannella M, Antonelli M, et al. Clinical experience of colistin-glycopeptide combination in critically ill patients infected with Gram-negative bacteria [J]. *Antimicrob Agents Chemother*, 2014, 58 (2): 851–858. DOI: 10.1128/AAC.00871-13.
- [29] Phee L, Hornsey M, Wareham DW. *In vitro* activity of daptomycin in combination with low-dose colistin against a diverse collection of Gram-negative bacterial pathogens [J]. *Eur J Clin Microbiol Infect Dis*, 2013, 32 (10): 1291–1294. DOI: 10.1007/s10096-013-1875-z.
- [30] Rigatto MH, Vieira FJ, Antochévis LC, et al. Polymyxin B in combination with antimicrobials lacking *in vitro* activity versus polymyxin B in monotherapy in critically ill patients with *Acinetobacter baumannii* or *Pseudomonas aeruginosa* infections [J]. *Antimicrob Agents Chemother*, 2015, 59 (10): 6575–6580. DOI: 10.1128/AAC.00494-15.
- [31] Kengkla K, Kongpakwattana K, Saokaew S, et al. Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis [J]. *J Antimicrob Chemother*, 2018, 73 (1): 22–32. DOI: 10.1093/jac/dkx368.
- [32] Liang QQ, Huang M, Xu ZJ. Early use of polymyxin B reduces the mortality of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection [J]. *Braz J Infect Dis*, 2019, 23 (1): 60–65. DOI: 10.1016/j.bjid.2018.12.004.
- [33] Juhász E, Iván M, Pintér E, et al. Colistin resistance among blood culture isolates at a tertiary care centre in Hungary [J]. *J Glob Antimicrob Resist*, 2017, 11: 167–170. DOI: 10.1016/j.jgar.2017.08.002.
- [34] Ergönül Ö, Aydın M, Azap A, et al. Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality [J]. *J Hosp Infect*, 2016, 94 (4): 381–385. DOI: 10.1016/j.jhin.2016.08.012.
- [35] Garnacho-Montero J, Amaya-Villar R, Ferrándiz-Millón C, et al. Optimum treatment strategies for carbapenem-resistant *Acinetobacter baumannii* bacteremia [J]. *Expert Rev Anti Infect Ther*, 2015, 13 (6): 769–777. DOI: 10.1586/14787210.2015.1032254.
- [36] Lim SK, Lee SO, Choi SH, et al. The outcomes of using colistin for treating multidrug resistant *Acinetobacter species* bloodstream infections [J]. *J Korean Med Sci*, 2011, 26 (3): 325–331. DOI: 10.3346/jkms.2011.26.3.325.
- [37] Daikos GL, Tsaousi S, Tzouveleki LS, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems [J]. *Antimicrob Agents Chemother*, 2014, 58 (4): 2322–2328. DOI: 10.1128/AAC.02166-13.
- [38] Zarkotou O, Pournaras S, Tselioti P, et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment [J]. *Clin Microbiol Infect*, 2011, 17 (12): 1798–1803. DOI: 10.1111/j.1469-0691.2011.03514.x.
- [39] Qureshi ZA, Paterson DL, Potoski BA, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens [J]. *Antimicrob Agents Chemother*, 2012, 56 (4): 2108–2113. DOI: 10.1128/AAC.06268-11.
- [40] Tumbarello M, Trecarichi EM, De Rosa FG, et al. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study [J]. *J Antimicrob Chemother*, 2015, 70 (7): 2133–2143. DOI: 10.1093/jac/dkv086.
- [41] Tal-Jasper R, Katz DE, Amrani N, et al. Clinical and epidemiological significance of carbapenem resistance in *Acinetobacter baumannii* infections [J]. *Antimicrob Agents Chemother*, 2016, 60 (5): 3127–3131. DOI: 10.1128/AAC.02656-15.
- [42] Dickstein Y, Leibovici L, Yahav D, et al. Multicentre open-label randomised controlled trial to compare colistin alone with colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative infections (AIDA): a study protocol [J]. *BMJ Open*, 2016, 6 (4): e009956. DOI: 10.1136/bmjopen-2015-009956.
- [43] Dalfino L, Puntillo F, Mosca A, et al. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study [J]. *Clin Infect Dis*, 2012, 54 (12): 1720–1726. DOI: 10.1093/cid/cis286.