

# 多黏菌素类联合其他抗菌药物治疗耐碳青霉烯类革兰阴性菌感染的研究进展

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**【摘要】**随着耐碳青霉烯类革兰阴性菌检出率不断增加, 多黏菌素类抗菌药物成为治疗耐碳青霉烯类革兰阴性菌感染的一种重要选择。但单一多黏菌素类抗菌药物治疗存在局限性, 如常规剂量效果不佳, 而增加剂量又会导致不良反应和耐药风险增加等。目前以多黏菌素类抗菌药物为基础的多药联合方案广泛应用于耐碳青霉烯类革兰阴性菌感染的治疗, 但最佳联合治疗方案, 以及不同联合治疗方案的安全性、有效性等尚无一致的定论。本文对基于多黏菌素类抗菌药物的联合用药方案在治疗耐碳青霉烯鲍曼不动杆菌、肺炎克雷伯菌和绿假单胞菌等革兰阴性菌感染的体内、体外研究进展进行综述, 以为多黏菌素类抗菌药物用于耐碳青霉烯类革兰阴性菌所致感染的治疗提供相关依据。

**【关键词】**多黏菌素; 耐碳青霉烯类革兰阴性菌; 联合用药

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## Research progress of Polymyxins combined with other antibiotics in the treatment of carbapenem-resistant gram-negative bacteria infection

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**【Abstract】**With the increasing detection rate of carbapenem resistant Gram-negative bacteria (CR-GNB), polymyxins (PMs) were to be the crucial escort in the treatment of CR-GNB infections. However, the single PM treatment has some limitations, such as insufficient efficacy at conventional doses and increasing the risk of adverse reactions and/or resistance when the dose increased. At present, PMs-based multi-drug combination regimens are widely used in the treatment of CR-GNB infection, however, there is still no consensus on the optimal combination regimen and the safety and effectiveness of different combination regimens. Therefore, this paper reviewed the *in vitro* and *in vivo* studies about combined drug regimen based on PMs in the treatment of CR-GNB infection, in order to provide relevant evidence for the application of PMs in the clinical treatment of CR-GNB-induced infection.

**【Key words】**Polymyxin; carbapenem resistant Gram-negative bacteria; drug combination

多黏菌素类(polymyxins, PMs)抗菌药物在20世纪50年代应用于临床, 因其肾毒性等不良反应逐渐被氨基糖苷类和喹诺酮类等抗菌药物替代<sup>[1]</sup>。近年

来, 由于耐碳青霉烯类革兰阴性菌(carbapenem resistant Gram-negative bacteria, CR-GNB)检出率不断增加, 主要是耐碳青霉烯类鲍曼不动杆菌(*Acineto-*

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*bacter baumannii*, AB)、以肺炎克雷伯杆菌(*klebsiella pneumoniae*, KP)为代表的肠杆菌和铜绿假单胞菌(*pseudomonas aeruginosa*, PA),使得多黏菌素类抗菌药物重新在临床抗革兰阴性菌感染治疗中发挥重要作用<sup>[1-3]</sup>。目前多黏菌素单药治疗,临床允许的最大剂量也较难达到药物代谢动力学目标值<sup>[4]</sup>,且易发生细菌异质性耐药,增加患者治疗失败风险<sup>[5]</sup>,多黏菌素与其他抗菌药物联合治疗成为研究热点。本文对以多黏菌素为基础的2种、3种药物联合治疗耐碳青霉烯类革兰阴性菌感染的研究进展进行归纳总结,以期多黏菌素联合用药的选择以及有效性和安全性提供参考依据。

## 1 多黏菌素类抗菌药物概述

### 1.1 临床常用多黏菌素类抗菌药物和剂量换算

目前临床常用的多黏菌素类抗菌药物包括多黏菌素B(polymyxins B, PMB)和多黏菌素E,又称黏菌素(colistin, COL),其中国内主要使用多黏菌素B,国外主要使用多黏菌素E<sup>[6-7]</sup>。临床使用的多黏菌素E包括注射用硫酸多黏菌素E和注射用多黏菌素E甲磺酸钠(Colistimethate Sodium, CMS),其中注射用多黏菌素E甲磺酸钠使用较多<sup>[1]</sup>。注射用多黏菌素E甲磺酸钠主要以国际单位或多黏菌素E基质(colistin base activity, CBA)作为剂量单位,不同国家的剂量单位不同,通常换算方法为:多黏菌素B 1 mg=1万国际单位;多黏菌素E甲磺酸钠 100万国际单位≈80 mg多黏菌素E甲磺酸钠≈33 mg多黏菌素E基质。硫酸多黏菌素E 1 mg≈2.27万国际单位<sup>[8-9]</sup>。除此之外,文献中未标明的多黏菌素E一般指多黏菌素E甲磺酸钠<sup>[5]</sup>。

### 1.2 不同多黏菌素类抗菌药物的特点和适应证

多黏菌素B和硫酸多黏菌素E可在人体内直接发挥药效,而多黏菌素E甲磺酸钠为前体药物,需要在体内转化为多黏菌素E后发挥作用<sup>[10]</sup>。多黏菌素E甲磺酸钠可在尿液中转化为多黏菌素E,使得多黏菌素E在尿液中浓度较高,因此尿路感染可优先选择多黏菌素E甲磺酸钠。与多黏菌素E相比,多黏菌素B具有更优的药物代谢动力学特性:由于多黏菌素E甲磺酸钠静脉注射后转化成具有活性的多黏菌素E需要一定

时间,因此很难在短时间达到所需的稳态血药浓度,而多黏菌素B是活性形式,因此对于侵袭性感染(如血流感染等)可优先选择多黏菌素B。此外,有部分研究表明多黏菌素B肾毒性更低<sup>[5, 11-12]</sup>。

## 2 以多黏菌素类抗菌药物为基础的两种抗菌药物联用治疗耐碳青霉烯类革兰阴性菌感染的研究进展

### 2.1 治疗耐碳青霉烯类鲍曼不动杆菌感染

**2.1.1 多黏菌素类联合美罗培南** 一项纳入406例患者的多中心、前瞻性随机对照研究(AIDA研究),分为多黏菌素E甲磺酸钠联合美罗培南治疗组( $n=208$ )与多黏菌素E甲磺酸钠单药治疗组( $n=198$ ),给药方案为多黏菌素E甲磺酸钠:负荷剂量900万国际单位,维持剂量每次450万国际单位,每日2次;美罗培南:每次2 g,每日3次(输注时间3 h),评价以耐碳青霉烯类鲍曼不动杆菌感染为主的肺炎或菌血症患者的临床疗效。结果显示,与单药治疗相比,联合治疗方案的14 d临床治疗失败率和14 d全因死亡率差异无统计学意义<sup>[13]</sup>。对从上述受试者中分离的包括131株鲍曼不动杆菌在内的171株临床分离株,进行多黏菌素E甲磺酸钠联合美罗培南的体外协同杀菌作用的体外研究,结果表明二者联用具有协同作用。上述研究结果表明,体外研究中存在协同杀菌作用的联合方案在临床实际治疗中,14 d临床治愈率并未优于单药治疗方案[调整OR值为0.52(95% CI:0.26~1.04)],换言之,两种抗菌药物的体外协同作用并不一定改善患者的临床结局<sup>[14]</sup>。

此外,一项纳入160例肺炎患者的回归性研究显示,多黏菌素E甲磺酸钠、美罗培南联合治疗组( $n=83$ )与多黏菌素E甲磺酸钠单药治疗组( $n=77$ )患者的14 d死亡率差异无统计学意义。对77例APACHE I评分>24分患者进行疾病严重程度调整后发现,联合治疗组患者( $n=50$ )14 d死亡率低于单药治疗组( $n=27$ )(9.1%比53.8%,  $P=0.020$ )<sup>[15]</sup>。另一项纳入71例菌血症患者的回顾性研究结果显示,多黏菌素E甲磺酸钠、美罗培南联合治疗组( $n=31$ )与多黏菌素E甲磺酸钠单药治疗组( $n=40$ )患者的14 d死亡率和临床治愈率未存在差异,但对于Pitt菌血症评

分 $\geq 4$ 分的患者,联合组与单药组的14 d死亡率差异有统计学意义(27.8%比66.7%)<sup>[16]</sup>。上述结果提示,多黏菌素类联用美罗培南治疗方案可考虑用于治疗耐碳青霉烯类鲍曼不动杆菌感染的重症患者。而体外研究所推荐的联合方案,其实际临床治疗结果尚需更多研究证实。

**2.1.2 多黏菌素类联合利福平** 3项随机对照研究(randomized controlled trial, RCT)对多黏菌素E甲磺酸钠、利福平联合方案的临床疗效进行评价。第1项RCT纳入209例耐碳青霉烯类鲍曼不动杆菌感染的肺炎患者,分为多黏菌素E甲磺酸钠、利福平联合治疗组( $n=104$ )与多黏菌素E甲磺酸钠单药组( $n=105$ )。结果显示,两组患者的30 d死亡率差异无统计学意义( $P=0.71$ ),联合治疗组病原体清除率存在优势( $P=0.034$ )<sup>[17]</sup>。第2项RCT纳入43例耐碳青霉烯类鲍曼不动杆菌感染的肺炎患者,联合治疗组与单药组30 d死亡率同样差异无统计学意义,而联合治疗组病原体清除时间更短( $P=0.029$ )<sup>[18]</sup>。第3项RCT只纳入9例患者,联合治疗组与单药组30 d死亡率差异亦无统计学意义<sup>[19]</sup>。上述研究结果显示,多黏菌素E甲磺酸钠、利福平联合方案存在病原体清除优势,但临床结局未显示出优势,需要进一步的临床研究。

## 2.2 治疗耐碳青霉烯类肺炎克雷伯菌为代表的肠杆菌感染

AIDA研究对耐碳青霉烯类肠杆菌的亚组分析结果显示,多黏菌素E甲磺酸钠、美罗培南联合治疗组与多黏菌素E甲磺酸钠组患者28 d死亡率差异无统计学意义[12/34(35%)比8/39(21%), $P=0.24$ ]<sup>[13]</sup>。另一项RCT纳入60例耐碳青霉烯肺炎克雷伯菌感染的肺炎患者,多黏菌素E甲磺酸钠、美罗培南联合治疗组与多黏菌素E甲磺酸钠单药治疗组患者医院内死亡率存在差异[43.3%(13/30)比16.7%(5/30), $P=0.047$ ]<sup>[20]</sup>。一项纳入661例耐碳青霉烯肺炎克雷伯菌感染患者(血流感染为主)的多中心队列研究,结果显示,包括美罗培南在内的治疗方案,若美罗培南的最低抑菌浓度 $\leq 8$  mg/L,与美罗培南单药治疗相比,联合治疗组14 d死亡率更低<sup>[21]</sup>。该队列研究的后续研究结果显示,美罗培南增大剂量(6 g/d,输注3 h),与美罗培南单药治疗相比,14 d生存率存在优势<sup>[22]</sup>。上述研究结果显示,若美罗培南最低抑菌浓度 $\leq 8$  mg/L,可考虑多

黏菌素类联合美罗培南(增大剂量/延长输注)的治疗方案。

## 2.3 治疗耐碳青霉烯类铜绿假单胞菌感染

2016年的一项多中心研究评估序贯吸入妥布霉素(每次300 mg,每日2次)和多黏菌素E(100万国际单位,每日2次)28 d对肺部耐碳青霉烯类铜绿假单胞菌感染的囊性纤维病患者治疗的有效性,共纳入36例患者,治疗时间为6个月。结果显示,与基线相比,患者1秒内用力呼气量(forced expiratory volume in one second, FEV1)增加9.1%( $P=0.004$ )<sup>[23]</sup>。另一项单中心研究,评价多黏菌素E(每次100万国际单位,每日2次)联合妥布霉素(每次300 mg,每日2次)治疗肺部耐碳青霉烯类铜绿假单胞菌感染囊性纤维病患者( $n=8$ )的有效性,治疗时间为28 d。结果显示,与基线相比,患者痰中铜绿假单胞菌减少2个数量级( $P=0.027$ )<sup>[24]</sup>。此外,一项纳入53例耐碳青霉烯类铜绿假单胞菌感染的慢性阻塞性肺疾病患者的回顾性研究显示,多黏菌素E、阿奇霉素联合治疗后,患者出现肺炎急性加重表现较未治疗下降38.3%<sup>[25]</sup>。一项RCT纳入285例耐碳青霉烯类铜绿假单胞菌感染的肺炎患者,根据治疗方案分为多黏菌素E、头孢他定、妥布霉素3药联合治疗组( $n=137$ ,多黏菌素E 100万国际单位,每日2次,治疗3个月;头孢他定静脉推注每次150 mg/kg,每日3次;妥布霉素静脉推注每次10 mg/kg,每日1次,治疗14 d)。多黏菌素E、环丙沙星2药治疗组( $n=148$ ,多黏菌素E 100万国际单位,每日2次;环丙沙星口服每次20 mg/kg,每日2次,治疗3个月),结果发现3个月时3药联合组患者耐碳青霉烯铜绿假单胞菌未清除率较2药组高(11.8%比4.3%, $P=0.037$ );患者入院率较两药组高(17.8%比6.3%, $P=0.003$ )<sup>[26]</sup>。上述结果均提示,对于耐碳青霉烯类铜绿假单胞菌感染,以多黏菌素类为基础的两种药物联合方案存在治疗优势,但尚需更多的临床研究证实。

## 3 以多黏菌素类抗菌药物为基础的3种抗菌药物联合治疗耐碳青霉烯类革兰阴性菌感染

目前对于部分难治性耐碳青霉烯类革兰阴性菌,



两种药物联合已不能达到抗感染治疗目的。其中一项纳入29项临床研究的Meta分析结果显示,多黏菌素E甲磺酸钠联合舒巴坦和替加环素对于耐碳青霉烯类鲍曼不动杆菌感染患者临床治愈率最高且肾毒性风险降低<sup>[27]</sup>。另一项纳入10例耐碳青霉烯的鲍曼不动杆菌感染重症呼吸机相关性肺炎患者的回顾性研究评估多黏菌素E静脉注射、吸入给药联合大剂量氨苄西林/舒巴坦和替加环素的临床治疗效果。给药方案为:静脉注射多黏菌素E负荷剂量900万国际单位,维持剂量每次450万国际单位、每日2次,吸入黏菌素每次200国际单位、每日3次;替加环素负荷剂量200 mg,维持剂量每次100 mg,每日2次;氨苄西林/舒巴坦每次9 g、每日3次。结果显示,全部患者实现14 d/28 d临床治愈,有1例患者发生急性肾损伤<sup>[28]</sup>。相对于3药联合的体外研究或动物体内研究,更多研究结果推荐多黏菌素类、美罗培南联合治疗耐碳青霉烯类革兰阴性菌感染患者<sup>[29-34]</sup>。

综上,以多黏菌素类抗菌药物为基础的3种药物联合方案存在抗感染治疗的优势,但同时具有不良反应、药物相互作用增加等潜在的风险。现有证据建议3种药物联合方案作为2种药物联合方案治疗不佳的后续选择。

#### 4 联合多黏菌素类抗菌药物雾化吸入治疗肺部感染

对于肺部感染患者,注射用多黏菌素类抗菌药物的临床最大耐受剂量不足以在肺组织体液中达到所需的药物浓度,吸入多黏菌素可作为一种联合选择<sup>[35-36]</sup>。有两项RCT评估抗菌药物联合多黏菌素吸入治疗的有效性和安全性,第一项RCT将100例呼吸机相关性肺炎患者分成多黏菌素E甲磺酸钠雾化吸入组(等价于75 mg多黏菌素E基质溶于4 mL雾化无菌生理盐水,每日2次, $n=51$ )和对照组(仅4 mL雾化无菌生理盐水,每日2次, $n=49$ )。引起感染的多重耐药革兰阴性菌中45%鲍曼不动杆菌和5%铜绿假单胞菌对碳青霉烯类耐药。结果显示,雾化吸入组的病原学结局较对照组差异有统计学意义( $P=0.03$ ),但临床结局差异无统计学意义<sup>[37]</sup>。第二项RCT将149例重症患者分为多黏菌素E甲磺酸钠雾化吸入组

(400万国际单位、每日3次, $n=73$ )和多黏菌素E甲磺酸钠静脉注射组(负荷剂量900万国际单位,维持剂量450万国际单位, $n=76$ ),两组均与美罗培南(每次1 g、每日3次)联合治疗。结果显示与静脉注射多黏菌素E甲磺酸钠相比,雾化吸入存在非劣性且肾毒性更低,14 d动脉血氧分压与吸入气氧浓度的比值存在显著改善( $P=0.012$ ),但重症监护病房住院时间及28 d死亡率差异无统计学意义<sup>[38]</sup>。上述研究结果显示,联合多黏菌素E甲磺酸钠雾化吸入存在临床治疗优势,但仍需进一步临床证据支持<sup>[39-40]</sup>。

综上,现有研究结果显示,以多黏菌素类抗菌药物为基础的两种抗菌药物联合方案具有显著的病原体清除方面优势,而较少存在临床治疗优势。其中多黏菌素类抗菌联合美罗培南治疗耐碳青霉烯类鲍曼不动杆菌感染患者的有效性研究数目最多,多数结果显示多黏菌素类抗菌、美罗培南联合方案的临床优势更多体现在重症患者。对于耐碳青霉烯类肺炎克雷伯杆菌感染的重症患者在美罗培南的 $MIC \leq 8$  mg/L时,PMs联合大剂量/延长输注的美罗培南效果更佳。对于耐碳青霉烯类铜绿假单胞菌引起的肺部感染患者,可以考虑联合吸入性多黏菌素类抗菌药物。对于多黏菌素类抗菌药物联合方案仍需进行大量研究,特别是高质量随机对照试验,评估联合治疗的有效性<sup>[41]</sup>。

值得注意的是,关于多黏菌素类药物联合治疗临床研究存在一定局限性:①多黏菌素类药物联合治疗临床研究多为回顾性研究,纳入患者的年龄、疾病严重程度(SOFA评分、APACHE II评分、重症监护病房治疗时间等)存在偏倚。②给药时机对预后影响较大<sup>[40,42-43]</sup>。③存在基础疾病的重症患者,治疗失败率较高,以全因死亡率作为主要结局指标可能不全面<sup>[44-45]</sup>。

#### 【参考文献】

- [1] Nation R, Li J, Cars O, et al. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus [J]. Lancet Infect Dis, 2015, 15 (2): 225-234.
- [2] Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria [J]. Clin Infect Dis, 2019, 69(Suppl 7): S521-S528.
- [3] Cerceo E, Deitelzweig SB, Sherman BM, et al. Multidrug-resistant gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerg-

- ing treatment options [J]. *Microb Drug Resist*, 2016, 22(5): 412-431.
- [4] Bergen PJ, Bulman ZP, Saju S, et al. Polymyxin combinations: pharmacokinetics and pharmacodynamics for rationale use [J]. *Pharmacotherapy*, 2015, 35(1): 34-42.
- [5] 中国医药教育协会感染疾病专业委员会, 中华医学会呼吸病学分会, 中华医学会重症医学分会, 等. 中国多黏菌素类抗菌药物临床合理应用多学科专家共识[J]. *中华结核和呼吸杂志*, 2021, 44(4): 292-310.
- [6] Pogue JM, Jones RN, Bradley JS, et al. Polymyxin susceptibility testing and interpretive breakpoints: recommendations from the United States Committee on Antimicrobial Susceptibility Testing (USCAST) [J]. *Antimicrob Agents Chemother*, 2020, 64(2): e01495-e15019.
- [7] Nang SC, Azad MAK, Velkov T, et al. Rescuing the Last-Line Polymyxins: achievements and challenges [J]. *Pharmacol Rev*, 2021, 73(2): 679-728.
- [8] Li ZF, Velkov T. Polymyxins: mode of action [M]. *Polymyxin Antibiotics: From Laboratory Bench to Bedside*, 2019: 37-54.
- [9] Nation RL, Li J, Cars O, et al. Consistent global approach on reporting of colistin doses to promote safe and effective use [J]. *Clin Infect Dis*, 2014, 58(1): 139-141.
- [10] Luque S, Escano C, Sorli L, et al. Urinary concentrations of colistimethate and formed colistin after intravenous administration in patients with multidrug-resistant gram-negative bacterial infections [J]. *Antimicrob Agents Chemother*, 2017, 61(8): e02595-e02616.
- [11] Kwa A, Ksaikou SK, Tam VH, et al. Polymyxin B: similarities to and differences from colistin (polymyxin E) [J]. *Expert Rev Anti Infect Ther*, 2007, 5(5): 811-821.
- [12] Zakuzn ZD, Suresh K. Rational use of intravenous polymyxin B and colistin: a review [J]. *Med J Malaysia*, 2018, 73(5): 351-359.
- [13] Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for 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.
- [14] Nutmana A, Lellouche J, Temkine E, et al. Colistin plus meropenem for carbapenem-resistant Gram-negative infections: in vitro synergism is not associated with better clinical outcomes [J]. *Clin Microbiol Infect*, 2020, 26(9): 1185-1191.
- [15] Shi H, Lee JS, Park SY, et al. Colistin plus carbapenem versus colistin monotherapy in the treatment of carbapenem-resistant acinetobacter baumannii pneumonia [J]. *Infect Drug Resist*, 2019, 12: 3925-3934.
- [16] Park SY, Si HJ, Eom JS, et al. Survival of carbapenem-resistant Acinetobacter baumannii bacteremia: colistin monotherapy versus colistin plus meropenem [J]. *J Int Med Res*, 2019, 47(12): 5977-5985.
- [17] Durante-Mangoni E, Signoriell OG, 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.
- [18] Aydemir H, Akdumand D, Pikin, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia [J]. *Epidemiol Infect*, 2013, 141(6): 1214-1222.
- [19] Park HJ, Cho JH, Kim HJ, et al. Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant Acinetobacter baumannii: a randomised controlled trial [J]. *J Glob Antimicrob Resist*, 2019, 17: 66-71.
- [20] Riethmuller J, Herrmann G, Graepler-Mainka U, et al. Sequential inhalational tobramycin-colistin-combination in CF-patients with chronic P. aeruginosa colonization – an observational study [J]. *Cell Physiol Biochem*, 2016, 39(3): 1141-1151.
- [21] Tumbarello M, Trecarichi EM, Derosa 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.
- [22] Giannella M, Trecarichi EM, Giacobbe DR, et al. Effect of combination therapy containing a high-dose carbapenem on mortality in patients with carbapenem-resistant Klebsiella pneumoniae bloodstream infection [J]. *Int J Antimicrob Agents*, 2018, 51(2): 244-248.
- [23] Abdelsalamm FA, Abdalla MS, El-Abharh SE. Prospective, comparative clinical study between high-dose colistin monotherapy and colistin-meropenem combination therapy for treatment of hospital-acquired pneumonia and ventilator-associated pneumonia caused by multidrug-resistant Klebsiella pneumoniae [J]. *J Glob Antimicrob Resist*, 2018, 15: 127-135.
- [24] Herrmann G, Yang L, Wu H, et al. Colistin-tobramycin combinations are superior to monotherapy concerning the killing of biofilm Pseudomonas aeruginosa [J]. *J Infect Dis*, 2010, 202(10): 1585-1592.
- [25] Monton C, Prina E, Pomares X, et al. Nebulized colistin and continuous cyclic Azithromycin in severe COPD patients with chronic bronchial infection due to pseudomonas aeruginosa: a retrospective cohort study [J]. *Int J Chron Obstruct Pulmon Dis*, 2019, 14: 2365-2373.
- [26] Hewers CL, Smyth AR, Brown M, et al. Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and pseudomonas aeruginosa infection: the Torpedo-Cfrc [J]. *Health Technol Assess*, 2021, 25(65): 1-128.
- [27] 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.
- [28] Assimakopoulos SF, Karamouzou V, Lefkaditi A, et al. Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant acinetobacter baumannii: a case series study [J]. *Infez Med*, 2019, 27(1): 11-16.
- [29] Diep JK, Jacobs DM, Sharma R, et al. Polymyxin B in combination with Rifampin and Meropenem against Polymyxin B-Resistant KPC-Producing Klebsiella pneumoniae [J]. *Antimicrob Agents Chemother*, 2017, 61(2): e02121-e02126.
- [30] Tangden T, Hickman RA, Forsberg P, et al. Evaluation of double- and triple-antibiotic combinations for VIM- and NDM-

- producing *Klebsiella pneumoniae* by in vitro time-kill experiments [J]. *Antimicrob Agents Chemother*, 2014, 58(3): 1757-1762.
- [31] Lagerback P, Khine WW, Giske CG, et al. Evaluation of antibacterial activities of colistin, rifampicin and meropenem combinations against NDM-1-producing *Klebsiella pneumoniae* in 24 h in vitro time-kill experiments [J]. *J Antimicrob Chemother*, 2016, 71(8): 2321-2325.
- [32] Fredborg M, Sondergaard TE, Wang M. Synergistic activities of meropenem double and triple combinations against carbapenemase-producing Enterobacteriaceae [J]. *Diagn Microbiol Infect Dis*, 2017, 88(4): 355-360.
- [33] Bulman ZP, Satlin MJ, Chen L, et al. New Polymyxin B dosing strategies to fortify old allies in the war against KPC-2-producing *klebsiella pneumoniae* [J]. *Antimicrob Agents Chemother*, 2017, 61(4): e02023-e02116.
- [34] Onufrak NJ, Smith NM, Satlin MJ, et al. In pursuit of the triple crown: mechanism-based pharmacodynamic modelling for the optimization of three-drug combinations against KPC-producing *Klebsiella pneumoniae* [J]. *Clin Microbiol Infect*, 2020, 26(9): e12561-e12568.
- [35] Cheah SE, Wang J, Nguyen VT, et al. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *pseudomonas aeruginosa* and *acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection [J]. *J Antimicrob Chemother*, 2015, 70(12): 3291-3297.
- [36] Vardaksa KZ, Voulgaris GL, Samonis G, et al. Inhaled colistin monotherapy for respiratory tract infections in adults without cystic fibrosis: a systematic review and meta-analysis [J]. *Int J Antimicrob Agents*, 2018, 51(1): 1-9.
- [37] Rattanaumpawan P, Lorsutthitham J, Ungprasert P, et al. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria [J]. *J Antimicrob Chemother*, 2010, 65(12): 2645-2649.
- [38] Abdellatif S, Trifi A, Daly F, et al. Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial [J]. *Ann Intensive Care*, 2016, 6(1): 26.
- [39] Jang JY, Kwon HY, Choi EH, et al. Efficacy and toxicity of high-dose nebulized colistin for critically ill surgical patients with ventilator-associated pneumonia caused by multidrug-resistant *Acinetobacter baumannii* [J]. *J Crit Care*, 2017, 40: 251-256.
- [40] Rello J, Sole-Lleonart C, Rouby JJ, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases [J]. *Clin Microbiol Infect*, 2017, 23(9): 629-639.
- [41] Feng JY, Peng CK, Sheu CC, et al. Efficacy of adjunctive nebulized colistin in critically ill patients with nosocomial carbapenem-resistant Gram-negative bacterial pneumonia: a multi-centre observational study [J]. *Clin Microbiol Infect*, 2021, 27(10): 1465-1473.
- [42] Kollef MH, Shorr AF, Bassetti M, et al. Timing of antibiotic therapy in the ICU [J]. *Crit Care*, 2021, 25(1): 360.
- [43] Ferrer R, Martin-Loeches I, Philips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program [J]. *Crit Care Med*, 2014, 42(8): 1749-1755.
- [44] Tsujib T, 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 Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP) [J]. *Pharmacotherapy*, 2019, 39(1): 10-39.
- [45] Falcone M, Russo A, Iacovelli A, et al. Predictors of outcome in ICU patients with septic shock caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* [J]. *Clin Microbiol Infect*, 2016, 22(5): 444-550.

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