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REVIEW

Treatment of Carbapenem-Resistant Gram-Negative Bacterial Infections with Polymyxins: A Review

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Abstract: Antimicrobial resistance poses a serious threat to human health. Polymyxins, as cyclic polypeptide antibiotics, include polymyxin B (PMB) and polymyxin E. Although they have different metabolic pathways, their antibacterial activities are similar. Polymyxins exert their effects through mechanisms such as disrupting bacterial cell membranes, neutralizing endotoxins, and impairing the respiratory chain. In clinical practice, polymyxins are often used in combination with other drugs to treat infections caused by carbapenem-resistant gram-negative bacteria (CRGNB). No difference in efficacy has been demonstrated between PMB and polymyxin E. An increasing amount of evidence suggests that combination therapy is not superior to monotherapy. The combination of intravenous administration and nebulization can help improve microbial clearance. Compared with other antibiotics, polymyxins have not shown obvious survival benefit. Polymyxins are associated with nephrotoxicity and neurotoxicity, and it is essential to closely monitor for related adverse events during the course of treatment.

Keywords: polymyxins, carbapenem-resistant gram-negative bacteria, hospital-acquired pneumonia, bloodstream infections, mortality

Introduction

Antimicrobial resistance (AMR), which includes multidrug resistance (MDR), extensively drug resistance (XDR), and pan-drug resistance (PDR), is a serious threat to human health worldwide.[1] Carbapenem-resistant Gram-negative bacilli (CRGNB) or carbapenem-resistant organisms (CRO) are defined as Gram-negative bacilli or organisms that are resistant to any carbapenem, documented to produce a carbapenemase or shown to carry a carbapenemase gene, including carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB).[2] CROs are usually XDR or PDR.[3] Infections caused by CRGNB are associated with high morbidity and mortality. As early as 2017, the World Health Organization (WHO) designated CRE, CRPA, and CRAB as "critical-priority" pathogens in the global priority list of antibiotic-resistant bacteria.[4] At present, carbapenem resistance represents a critical and escalating global threat.

From EARS-Net data collected between Jan 1, 2015, and Dec 31, 2015, 671689 infections with antibiotic-resistant bacteria were estimated, and 67.9% of the total disability-adjusted life-years (DALYs) per 100000 were caused by infections with four antibiotic-resistant bacteria: third-generation cephalosporin-resistant *Escherichia coli*, meticillin-resistant *Staphylococcus aureus* (MRSA), CRPA, and third-generation cephalosporin-resistant *Klebsiella pneumoniae*.[5] The rate for CRO was 29 cases per 100,000 population in Alameda County, USA, and cases significantly increased over the 2-year period.[2] The CHINET surveillance results showed that the detection rate of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in China increased from 3.0% in 2005 to 20.9% in 2017.[6] Between June 2019 and February 2021, in 333 ICUs across 52 countries, among 2,600 patients with hospital-acquired bloodstream infections (HA-BSI), the proportion of CRKP reached 37.8%.[7] Among *Klebsiella pneumoniae* isolates from patients admitted to Ramadi Teaching

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Hospital, Al-Anbar Governorate, 20% were metallo-β-lactamase producers; likewise, 33.0% of resistant *Pseudomonas aeruginosa* isolates carried metallo-β-lactamases, and 87.5% of *Burkholderia cepacian* and *Aeromonas sobria* isolates produced carbapenemases.[8–10] The WHO priority antimicrobial resistance phenotype (WPAP) bacteria, particularly CRKP and CRAB, are frequently detected in healthcare-associated BSIs in Brazil, making them a major public health issue in the country.[11] Worldwide, across 204 countries and territories, deaths associated with carbapenem resistance rose from 619,000 in 1990 to 1,030,000 in 2021, while deaths directly attributed to carbapenem resistance increased from 127,000 to 216,000 over the same period.[12] In 2019, globally, CRAB caused 50,000–100,000 deaths.[13] The CRACKLE-2 cohort study showed that from June 2017 to November 2018, the unadjusted 30-day all-cause mortality rate among patients with CRKP infection was 19%, and the unadjusted 90-day all-cause mortality rate was 22%.[14]

CRKP, CRAB, and CRPA are common CRGNB that are sensitive to polymyxins.[4] Polymyxins are often used in combination with carbapenems, tigecycline, fosfomycin, and sulbactam.[15] The efficacy and safety of polymyxins remain to be further elucidated. This article elaborates on the types, safety, and efficacy of polymyxins.

Types of Polymyxins

Polymyxins are cyclic polypeptide antibiotics, primarily consisting of five types: A, B, C, D, and E. Only polymyxin B (PMB) and polymyxin E, which have similar structures, are used clinically.[16] The common formulation of PMB is polymyxin B sulfate, while polymyxin E is commonly available as colistin sulfate and colistin methanesulfonate (CMS). Polymyxin E and polymyxin B differ in the amino acid of the peptide ring (R2 group), with a phenylalanine in PMB and a leucine in colistin (Figure 1).[17] CMS, as the most widely used form of polymyxin E, has its positively charged group masked by the negatively charged methanesulfonate moiety at physiological pH. It acts as an inactive prodrug that can be converted in aqueous media as well as in biological fluids. It exhibits lower toxicity compared to colistin sulfate. In contrast, PMB, as an active antibiotic, can be administered directly.[18] In Europe and Australia, only CMS is available, while clinicians in the United States, Brazil, Malaysia, and Singapore have access to both CMS and PMB.[17]

60%–70% of CMS is excreted via the kidneys, with an variable elimination half-life of 2–12 hours affected by multiple factors. The active metabolite of CMS, polymyxin E, is mostly reabsorbed by the renal tubules, with only 1% being excreted via the kidneys and a renal clearance rate of 1.9 mL/min. PMB is also largely reabsorbed by the renal tubules, with only 4% being excreted via the kidneys, and it reaches peak plasma concentrations immediately after infusion. Critically ill patients, renal dysfunction, intermittent hemodialysis, and continuous renal replacement therapy (CRRT) significantly affect the pharmacokinetics of CMS, and both CMS and polymyxin E can be cleared by renal

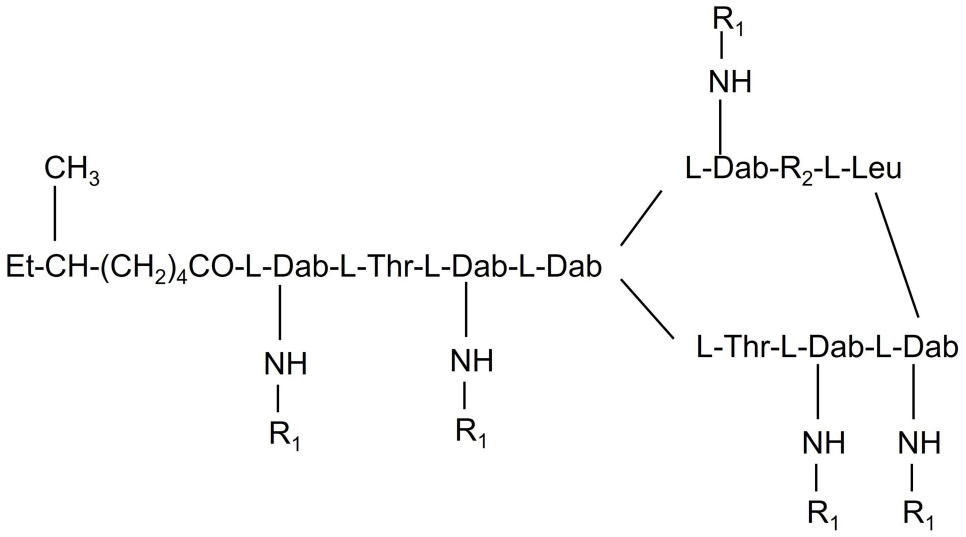

Figure 1 Chemical Structure of Polymyxins. Polymyxin B R1 = H, R2 = D-Phe; Polymyxin E R1 = H, R2 = D-Leu; CMS: R1 = -CH2-SO3H, R2 = D-Leu.
Abbreviations: CMS, colistin methanesulfonate; Dab, Diaminobutyric acid; Thr, Threonine; Phe, Phenylalanine; Leu, Leucine; L, Levogyre; D, Dextrogyre; ET, Ethyl group.

replacement therapies.[19] Achieving therapeutic colistin concentrations may be challenging for patients with normal renal function due to the rapid clearance of the prodrug CMS.[20]

PMB requires an initial loading dose of 2.0–2.5 mg/kg, followed by a maintenance dose of 2.5–3 mg/kg per day administered in two divided doses, with each infusion lasting more than 1 hour. Dose adjustment based on renal function is not necessary.[21] The loading dose of CMS is 5 mg/kg of colistin base activity (CBA), with a maximum dose not exceeding 300 mg CBA, administered via continuous intravenous infusion for more than 0.5–1 hour. After 12–24 hours, a maintenance dose of 2.5–5 mg/kg per day CBA is given, divided into 2–4 doses per day. Dose adjustment based on renal function is required. The specific dose adjustment methods are shown in Table 1.[19]

Mechanism of Antibacterial Action

Polymyxins are bactericidal agents whose antibacterial activity is exerted through disruption of the bacterial cell membrane, leading to cell lysis.[20] The antimicrobial spectrum of polymyxins is presented in Table 2.

Polymyxins can interact with the negatively charged lipid A of lipopolysaccharide (LPS) on the bacterial cell membrane through their positively charged groups, leading to increased membrane permeability. This interaction causes the leakage of small molecules such as purines and pyrimidines from the cell, resulting in bacterial swelling, dissolution, and ultimately death. Additionally, polymyxins have hydrophobic regions, such as fatty acyl chains, which can interact with corresponding regions of LPS, further increasing membrane permeability.[17] Polymyxins can also induce the fusion of the inner leaflet of the outer membrane with the outer leaflet of the cytoplasmic membrane, leading to loss of phospholipids and cell death.[22]

Polymyxins possess the ability to neutralize endotoxins and can inhibit bacterial respiratory enzymes [type II NADH-quinone oxidoreductases (NDH-2)] in the bacterial inner membrane, resulting in rapid cell death.[23] In addition to providing rapid bactericidal activity, polymyxins also have the ability to enhance the activity of other classes of antibiotics.[19]

Table 1 Daily Dose of CMS

Creatinine Clearance, mL/Minute	Daily Dose (CBA, mg/d)	Million IU/day
0	130	3.95
5–10	145	4.40
10–20	160	4.85
20–30	175	5.30
30–40	195	5.90
40–50	220	6.65
50–60	245	7.40
60–70	275	8.35
70–80	300	9.00
80–90	340	10.30
≥90	360	10.90

Abbreviation: CMS, colistin methanesulfonate.

Table 2 Antimicrobial Spectrum of Polymyxins

Active	*Enterobacteriaceae* family	*Escherichia coli, Enterobacter spp., Klebsiella spp., Citrobacter spp.,Salmonella spp., and Shigella spp.*
	Nonfermentative Gram-negative bacteria	*Acinetobacter baumannii, Pseudomonas aeruginosa, and Stenotrophomonas maltophilia*
Non-Active	Naturally resistant to polymyxins	*Proteus spp., Morganella morganii, Providencia spp., Serratia marcescens, Pseudomonas mallei, Burkholderia cepacia, Chromobacterium spp., Edwardsiella spp., Brucella, Legionella, Campylobacter, and Vibrio cholerae.*
	Others	Gram-positive bacteria *(Neisseria spp.)*, Gram-positive bacteria,anaerobic bacteria

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Efficacy of Polymyxins

PMB and Polymyxin E

PMB and polymyxin E are both used to treat infections caused by CRGNB. A retrospective cohort study conducted in Brazil from 2014 to 2021 showed that, compared with CMS, PMB had no different impact on 30-day mortality in the treatment of BSIs [adjusted hazard ratio (aHR)=0.82; 95% confidence interval (CI):0.52–1.30; p=0.40].[24] The study enrolled 259 BSI cases, the predominant pathogens being CRPA and CRAB. Consistently, a second retrospective analysis spanning 2016–2021 yielded parallel findings in CRKP bacteremia. The results showed that the 30-day mortality rates were 38.8% (17/46) in the CMS group and 44.6% (25/54) in the polymyxin B group, with no statistically significant difference (p=0.54).[25]

Conversely, some investigations have reported divergent findings. An observational prospective study compared the efficacy and safety of CMS and PMB in the treatment of multidrug-resistant gram-negative bacterial infections. In this study, CMS doses were adjusted according to renal function. The results showed that the clinical response rate (67.6% vs 37%;p < 0.001) and microbiological eradication rate (73.1% vs 46.3%;p = 0.001) were significantly higher in the CMS group than in the PMB group. The all-cause mortality rate was lower in patients treated with CMS than in those treated with PMB (19.4% vs 42.6%, p = 0.002).[26] Discrepancies in dosing regimens across the study cohorts may account for the divergent outcomes observed. Meta-analysis showed that there was no significant difference in the unadjusted mortality rate between patients treated with CMS and those treated with PMB [risk ratio(RR)=0.71;95% CI:0.45–1.13; I^2 = 80%).[27] An I^2 of 80% indicates substantial heterogeneity among studies, attributable to factors such as pathogen species, infection site, and prescribed dosage.

A retrospective study has shown that in the treatment of carbapenem-resistant gram-negative bacilli infections, colistin sulfate demonstrated a significantly higher microbial efficacy (57.1%) compared to PMB (30.8%) (p=0.022).[28] However, other study have indicated no significant difference (44.0% vs 36.5%;p=0.402).[29] The two studies had comparable sample sizes; however, the first enrolled patients with infections at any site, whereas the second was restricted to pulmonary infections. In both, no difference in mortality was observed between the two treatment arms.

Monotherapy Vs Combination Therapy

Polymyxins can be administered either as monotherapy or in combination with other antibiotics. However, an increasing number of studies have shown that there is no advantage of polymyxin combination therapy over polymyxin monotherapy.

A retrospective cohort study in 2017 showed that, in the treatment of CRE infections, patients who received combination therapy containing CMS had a lower mortality rate than those receiving monotherapy in the high-mortality risk group [48% (30/63) vs 62% (64/103); aHR=0.56,95% CI: 0.34–0.91; p=0.02]. However, there was no advantage in the low-mortality risk group [24% (17/72) vs 20% (21/105); aOR=1.21,95% CI:0.56–2.56; p=0.62].[30] On the contrary, in a randomized, double-blind, controlled trial comparing CMS monotherapy with CMS combined with meropenem for the treatment of pneumonia and bloodstream infections caused by CRGNB, there were no significant differences between the two groups in terms of mortality rate (43% vs 37%;p=0.17), clinical failure rate (65% vs 58%, difference 6.8%, 95% CI: −3.1–16.6), microbiological cure rate (65% vs 60%, difference 4.8%, 95% CI: −5.6–15.2), or adverse events (incidence of acute kidney injury, 52% vs 49%, P=0.55), indicating that the combination of CMS and meropenem is not superior to CMS monotherapy for treating pneumonia or bloodstream infections caused by these pathogens.[18] These findings were corroborated by an additional randomized controlled trial in which adults with CRGNB infections were randomly assigned to receive either CMS alone or CMS combined with meropenem. Fourteen days after randomization, there was no significant difference in clinical failure between CMS monotherapy (156/198, 79%) and combination therapy (152/208, 73%) (risk difference −5.7%, 95% CI: −13.9 to 2.4).[31] Similarly, in the treatment of CRE infections, combination therapy with CMS and fosfomycin showed no advantage over CMS monotherapy when assessed by 30-day mortality (aOR=1.51;95% CI:0.60–3.78;p=0.383).[32] Even with in vitro synergy, combination therapy with CMS and meropenem showed no benefit over CMS monotherapy in terms of 14-day clinical failure (aOR=0.76;95% CI:0.31–1.83) or 14-day mortality (aOR=0.76;95% CI:0.19–3.10) in treating severe CRGNB infections.[33] Moreover, a secondary analysis of a randomized controlled trial examining the efficacy of CMS alone versus CMS in combination

with meropenem for treating CRAB infections showed that patients receiving CMS in combination with meropenem had a higher mortality rate than those receiving CMS monotherapy (OR=3.065;95% CI:1.021–9.202).[34] This study included only 52 patients with colistin-resistant isolates.

A meta-analysis including 62 studies with 8,342 patients showed that, in the treatment of CRGNB infections, monotherapy was associated with higher mortality (OR=1.29;5% CI:1.11–1.51), lower clinical success rates (OR=0.74;95% CI:0.56–0.98), and lower microbial eradication rates (OR=0.71;95% CI: 0.55–0.91).[35] Nevertheless, the majority of the studies pooled in this meta-analysis were observational. A Bayesian analysis included randomized controlled trials compared CMS-meropenem combination therapy with CMS monotherapy for CRAB infections. The overall probability of a clinically meaningful mortality benefit was low: the summary relative risk ranged from 0.99 to 1.03, and the probability that the combination reduced mortality was only 40.5%–53.5%, with a medium probability of 14.0%–22.6%. Thus, adding meropenem to CMS is unlikely to confer a meaningful survival advantage.[36]

To date, studies investigating combination therapy have yielded discordant results, probably reflecting heterogeneity in trial design and patient populations. Observational designs are susceptible to unmeasured confounders that can distort effect estimates; consequently, randomized controlled trials furnish the higher attainable evidence. On current evidence, combination therapy has not demonstrated any superiority.

Intravenous Polymyxins Alone Vs Combination with Nebulization

Studies have shown that nebulized polymyxins can increase drug concentrations in the alveolar epithelial lining fluid.[37] Current evidence indicates that clinicians will consider adding nebulized polymyxins when dealing with ventilator-associated pneumonia(VAP) caused by CRGNB susceptible to polymyxins.[37–42] During nebulized polymyxin administration, treatment-associated bronchospasm requires careful monitoring. Both colistin sulfate and CMS can be used for nebulization therapy, but colistin sulfate is associated with a higher frequency of bronchospasm.[23] To minimize the incidence of bronchospasm and ensure optimal aerosol delivery, airway suctioning and prophylactic inhaled bronchodilator should be completed ≥30 minutes before nebulized polymyxins is initiated.[40] Bronchospasm attributable to nebulized polymyxins promptly remits after drug withdrawal and administration of an inhaled β_2-agonist.[43,44] Meta-analysis showed that, among 132 patients receiving adjunctive nebulized polymyxins, seven developed bronchospasm (5.30%), compared with only one of 148 control subjects (0.07%) (OR=5.19;95% CI:1.05–25.52; p = 0.04).[39]

A case-control study including 208 patients with VAP showed that the clinical cure rate was higher in the group treated with combined intravenous and nebulized CMS compared to those treated with intravenous CMS alone, with rates of 69.2% and 54.8%, respectively (p=0.03). Additionally, the number of days on mechanical ventilation was fewer in the combined treatment group, with 8 days compared to 12 days in the intravenous-only group (P=0.001).[38] However, a prospective multicenter cohort study showed compared to intravenous PMB alone, aerosolized and intravenous PMB did not lead to statistically significant improvements in microbiological outcome (42.9%vs 62.1%; p=0.141) and 28-day mortality (25.7% vs 27.6%;p=0.919).[40] In the combination group, the inhalation dose of polymyxin B was 25 mg dissolved in 5 mL of sterile water, administered every 12 h. Importantly, with only 64 enrolled subjects, the study was markedly under-powered and thus prone to a false-negative finding. Consistently, in a randomized control trial, treatment success was nonsignificantly higher in PMB plus high-dose colistin nebulization group (63.66 vs 30.77%; p = 0.217) when compared with the intravenous PMB alone group.[42] Similarly, this study was hampered by an extremely small sample size.

A meta-analysis that included 7 observational studies and 3 randomized controlled trials showed that compared to intravenous CMS alone, the combination of nebulized and intravenous CMS demonstrated a higher microbial eradication rate (OR=2.21; 95% CI:1.25–3.92) and similar nephrotoxicity (OR=0.86; 95% CI:0.60–1.23). However, there were no significant differences in clinical response (OR=1.39; 95% CI:0.87–2.20), mortality (OR=0.74; 95% CI:0.50–1.12), or duration of mechanical ventilation (mean difference (MD)=−2.5; 95% CI:- 5.20–0.19). The risk of bronchospasm was significantly higher in the nebulized polymyxins group (OR=5.19; 95% CI:1.05–25.52).[39] This study did not differentiate between the various polymyxins administration modalities. A subsequent network meta-analysis overcame this limitation. The results showed that compared to intravenous polymyxins alone, the combination of intravenous and nebulized polymyxins significantly reduced patient mortality (OR=0.67; 95% CI:0.50–0.88) and improved microbial eradication

rates (OR=2.70;95% CI:1.90–3.90).[41] The second meta-analysis incorporated a larger number of studies and patients and employed a network meta-analytic framework, thereby delivering more comprehensive evidence.

Owing to variability in trial design, pathogens, sample size, and patient populations, studies evaluating adjunctive nebulized polymyxins have reported heterogeneous outcomes. Pending definitive evidence, nebulized polymyxins may be a reasonable adjunctive therapy for VAP caused by CRO, but vigilance for procedure-related bronchospasm is essential.

Polymyxins Versus Other Antibiotics

Compared with other antibiotics, polymyxins show varying efficacy in the treatment of infections caused by CRGNB in different studies.

A retrospective study including adult patients with CRE bacteremia treated with ceftazidime-avibactam or CMS from September 2017 to December 2020 showed no difference in 30-day mortality (aHR=0.50;95% CI:0.20–1.21;p=0.12).[45] Notably, the cohort comprised only 61 patients. Among CRKP-infected individuals, ceftazidime-avibactam achieved higher clinical efficacy (71.3% vs 56.1%; $p = 0.011$) and microbiological clearance (74.7% vs 41.4%; $p < 0.001$) and reduced acute kidney injury (13.5% vs 33.7%; $p < 0.001$) compared with PMB, yet mortality remained comparable.[46] These findings align with a separate investigation in which ceftazidime-avibactam again achieved superior microbial clearance relative to PMB in CRE infections (p=0.012), yet mortality outcomes remained statistically indistinguishable between the two treatment arms (p=0.961).[23] A meta-analysis including 10 articles with 833 patients with CRE infections showed that patients treated with ceftazidime-avibactam had significantly lower 30-day mortality (RR = 0.49, 95% CI 0.01–2.34;p<0.00001), higher clinical cure rates (RR=2.70, 95% CI 1.67–4.38;p<0.00001), and higher microbiological eradication rates (RR = 2.70, 95% CI:2.09–3.49;p<0.00001) compared with those treated with polymyxins.[47]

The ATTACK study compared the efficacy and safety of sulbactam-durlobactam in combination with imipenem/cilastatin versus CMS in combination with imipenem/cilastatin for the treatment of CRAB infections. After adjustment for randomization stratification factors, the difference in 28-day all-cause mortality between the two groups was −13.8% (95% CI:-29.3–1.6). This demonstrated that sulbactam–durlobactam was non-inferior to colistin.[48] Observational studies have reported concordant findings. In patients with CRAB infections, those treated with CMS had a higher 30-day mortality rate compared to those treated with cefiderocol. The mortality rates were 55.8% and 34.0%, respectively (p=0.018) and cefiderocol therapy was protective in an inverse probability of treatment weighting (IPTW) analysis (HR=0.44, 95% CI: 0.22–0.66, $p < 0.001$).[49] Being an observational, retrospective study with a modest sample size, the second investigation has limited external validity.

In a randomized controlled study including patients with hospital-acquired/ventilator-associated pneumonia, complicated intra-abdominal infections, or complicated urinary tract infections caused by imipenem-insensitive gram-negative pathogens, 31 patients received imipenem/relebactam, and 16 patients received CMS in combination with imipenem/cilastatin. The results showed that for favorable overall response (90% CI for difference:–27.5–21.4) and 28-day mortality (90% CI for difference:–46.4–6.7), there was no significant difference between CMS in combination with imipenem/cilastatin and imipenem/relebactam in the treatment of Gram-negative infections.[50] These observations have subsequently been corroborated by a multicenter prospective randomized trial conducted at 32 centers in Europe compared the efficacy and safety of CMS and meropenem in patients with late-onset VAP (VAP occurring after 96 hours of mechanical ventilation). Both treatments were combined with levofloxacin. The results showed no significant difference in mortality between the CMS group (19/82, 23.2%) and the meropenem group (19/75, 25.3%). The risk difference between the two groups was −2.16% (−15.59% to 11.26%;p=0.377), which exceeded the non-inferiority margin of 10%.[51] However, this study was not restricted to CRO infections. In the treatment of VAP, a meta-analysis showed that the cure rate in the CMS group increased by 1.9% (range: +16% to −10.5%), with a post-hoc non-inferiority threshold of −10.5% (pooled risk ratio = 0.895) compared to standard care. This supports the use of CMS for VAP, especially when nebulized and intravenous formulations are used in combination.[52]

Pharmacokinetic studies have shown that when using polymyxins, attention should be paid to the drug's AUC (area under the curve). Current guidelines recommend targeting an area under the plasma concentration-time curve across 24 hours at steady state (AUCss,24h) of ~50 mg·h/L for colistin, equivalent to an average steady-state plasma

concentration (Css,avg) of ~2 mg/L total drug. Some evidence indicates that an AUCss,24h target of 50–100 mg·h/L, corresponding to a C ss,avg of 2–4 mg/L, may be acceptable from a toxicity standpoint.[19] A prospective observational multicenter study showed that an AUC greater than 50 mg·h/L is associated with reduced mortality in patients with intra-abdominal infections but not in patients with lower respiratory tract infections.[53] A single-center retrospective analysis suggested that survival benefit emerges only when the polymyxins AUCss,24 h exceeds 81.6 mg·h/L.[54] However, the majority of studies have not conducted drug concentration monitoring for polymyxins.

Current evidence indicates that, compared with alternative agents, polymyxins does not increase mortality in patients with CRO infections and remains a viable therapeutic option; nevertheless, therapeutic drug monitoring (TDM) is warranted during treatment.

Safety of Polymyxins

Polymyxins have a narrow therapeutic window, and the major adverse reactions associated with intravenous use are neurotoxicity and nephrotoxicity, such as paresthesia, visual disturbances, mental confusion, ataxia, neuromuscular blockade, apnea, and acute kidney injury.[23] Both CMS and PMB are cytotoxic to renal tubular cells, which can lead to acute tubular necrosis. Nephrotoxicity is associated with higher doses and longer durations of treatment, with overall incidence rates ranging from 0% to 55%.[16,20]

A retrospective study has shown that among 178 patients treated with CMS for more than 48 hours, the incidence of nephrotoxicity was 44.9%. Mortality was significantly higher in patients with nephrotoxicity. Higher doses of CMS and earlier onset of renal injury were associated with a higher proportion of dialysis. However, this nephrotoxicity is reversible and rarely causes permanent damage, with an average time to return to baseline of 7 ± 8 days.[55]

When comparing imipenem/relebactam with CMS in combination with imipenem/cilastatin, the incidence of nephrotoxicity was 10% and 56%, respectively (p=0.002), indicating a higher nephrotoxicity with CMS.[50] Consistently, a separate study reported comparable findings. Compared with meropenem in combination with levofloxacin, CMS in combination with levofloxacin increased the incidence of renal failure, with rates of 18.8% and 33%, respectively (p=0.012). The proportion of patients requiring renal replacement therapy was also higher, at 1.8% and 9.1%, respectively (p=0.015).[51]

In a comparison of the safety of sulbactam-durlobactam in combination with imipenem/cilastatin versus CMS in combination with imipenem/cilastatin for the treatment of CRAB infections, the incidence of nephrotoxicity was significantly lower in the sulbactam-durlobactam group compared to the CMS group (13% 12/91 vs 38% 32/85; p<0.001).[48] However, a multicenter retrospective study showed that, compared with ceftazidime-avibactam, CMS did not have higher nephrotoxicity, with the incidence of acute kidney injury being 9.4% and 10.3%, respectively (p=0.61).[56] It should be noted, however, that the study comprised only 61 patients and observational. A meta-analysis including 7 retrospective studies and 4 prospective cohort studies with 1,111 patients with CRE infections showed that ceftazidime-avibactam had lower nephrotoxicity than polymyxins (RR = 0.42; 95% CI:0.23–0.77; p < 0.05).[57]

Whereas a prospective observational study detected no significant difference in nephrotoxicity between CMS and PMB (59.3% vs 55.6%, P = 0.653), a retrospective cohort reported a markedly lower incidence of acute kidney injury(AKI) with PMB than with CMS (34.7% vs 52.6%; p = 0.013).[26,58] Extending this comparison to CRKP infections, a multivariable analysis that adjusted for Pitt bacteremia score and primary infection site again revealed no significant difference in AKI rates between the two agents (CMS 47.8% vs PMB 57.4%, P = 0.8).[25] Dose adjustment of colistin based on creatinine clearance and the heterogeneous AKI definitions across studies are key drivers of the reported variability in AKI incidence. Meta-analyses suggest that, compared with PMB, CMS is associated with more frequent and faster-onset nephrotoxicity (HR=2.16;95% CI:1.43–3.27).[27] Besides, compared with intravenous CMS, no differences in AKI were observed between groups treated with nebulized and intravenous CMS (p=0.62).[38] However, when doses are adjusted according to creatinine clearance, the safety profile of CMS is comparable to that of β-lactam antibiotics (33% vs 15.3%) and superior to that of PMB (59.3% vs 55.6%;p = 0.653).[26,59]

When prescribing polymyxins, the possible emergence of resistance must be kept in mind. Their use has been shown to increase the carriage rate of mobile colistin-resistance genes among CRE, and a sharp rise in colistin resistance has already been documented.[60,61] Up to 51.3% of CRKP isolates are now reported to be colistin-resistant, and one

prospective study detected the development of colistin resistance in 10.3% of patients during or shortly after polymyxin therapy.[62,63]

Polymyxins are intrinsically nephrotoxic and carry the additional risk of resistance induction; therefore, renal function must be closely monitored and colistin dose should be promptly adjusted to creatinine clearance.

Conclusions and Future Perspectives

The situation of bacterial resistance is severe and poses a serious threat to human health. As bactericidal agents, both CMS and PMB can be used to treat CRGNB infections. No efficacy advantage of polymyxin B over polymyxin E has been demonstrated, and accumulating evidence indicates that combination therapy is not superior to monotherapy. The combination of nebulized and intravenous polymyxins can improve microbial eradication rates and clinical cure rates. Polymyxins have not conferred a clear survival benefit compared with other antibiotics. Close attention should be paid to the emergence of resistance during treatment. With the relatively high mortality in polymyxin treated infections, we have not found the ideal drugs to treat these infections. TDM of polymyxins is rapidly evolving from a "desirable option" to a cornerstone of precision medicine. Future efforts should focus on developing predictive models for the efficacy and safety of polymyxins to identify patients who may benefit from their use while avoiding injury.

Disclosure

The authors report no conflicts of interest in this work.

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