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Efficacy of polymyxins in the treatment of carbapenem-resistant *Enterobacteriaceae* infections: a systematic review and meta-analysis

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ABSTRACT

In recent years, carbapenem-resistant *Enterobacteriaceae* has become endemic in many countries. Because of limited treatment options, the abandoned "old antibiotics", polymyxins, have been reintroduced to the clinic. To evaluate the clinical efficacy of polymyxins in the treatment of infections caused by carbapenem-resistant *Enterobacteriaceae*, we systemically searched the PubMed, Embase, and Cochrane Library databases and analyzed the available evidence. The Preferred Reporting Items for Systematic reviews and Meta-Analysis statement were followed, and the I^2 method was used for heterogeneity. Nineteen controlled and six single-arm cohort studies comprising 1086 patients met the inclusion criteria. For controlled studies, no significant difference was noted for overall mortality (OR, 0.79; 95% CI, 0.58–1.08; $p = 0.15$), clinical response rate (OR, 1.24; 95% CI, 0.61–2.54; $p = 0.55$), or microbiological response rate (OR, 0.59; 95% CI, 0.26–1.36; $p = 0.22$) between polymyxin-treated groups and the control groups. Subgroup analyses showed that 28-day or 30-day mortality was lower in patients who received polymyxin combination therapy than in those who received monotherapy (OR, 0.36; 95% CI, 0.19–0.68; $p < 0.01$) and the control groups (OR, 0.49; 95% CI, 0.31–0.75; $p < 0.01$). The results of the six single-arm studies were in accordance with the findings of controlled studies. One controlled and two single-arm studies that evaluated the occurrence of nephrotoxicity reported a pooled incidence rate of 19.2%. Our results suggest that polymyxins may be as efficacious as other antimicrobial therapies for the treatment of carbapenem-resistant *Enterobacteriaceae* infection. Compared to polymyxin monotherapy, combination regimens may achieve lower 28-day or 30-day mortality. Future large-volume, well-designed randomized control trials are required to determine the role of polymyxins in treating carbapenem-resistant *Enterobacteriaceae* infections.

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Introduction

In recent years, carbapenemase-producing *Enterobacteriaceae*, the majority of which is carbapenem-resistant (CRE), have posed a great threat to public health.[1] Outbreaks and increased prevalence due to these notorious superbugs have been continuously reported in hospitals worldwide, resulting in high mortality.[2] Production of *Klebsiella pneumoniae* carbapenemase (KPC) enzymes is the most common mechanism of resistance, while the incidence of zinc-dependent metallo-β-lactamases (VIM, IMP, and NDM types) is also increasing.[3] The carbapenemase-producing strains can exhibit resistance to most clinically available β-lactams, as well as other important antimicrobial classes such as aminoglycosides and fluoroquinolones.[4] Multidrug-resistant (MDR) *Enterobacteriaceae* make the empiric choice of appropriate antimicrobial treatment very difficult; moreover, the best approach for treating CRE infections is not currently known.

Polymyxins, a group of polypeptide antibiotics, demonstrate potent antimicrobial activity against MDR Gram-negative bacteria by disrupting the outer membrane.[5] They were abandoned in the 1960s because of severe adverse effects[5]; however, limited options for treating infections caused by MDR Gram-negative bacteria have forced clinicians to reuse old drugs.[6] So far, many clinical studies have evaluated the efficacy of polymyxins in the treatment of CRE infections, yielding various results. Furthermore, the significant pharmacokinetic deficiencies of polymyxins and the rapid emergence of resistance during treatment have led many clinicians to embrace combination regimens as the preferred treatment strategy for CRE infections.[7] Nonetheless, the important question on whether combination therapy, which may increase toxicity and cost, can bring more benefit than monotherapy remains unanswered.

Therefore, in this study, we systemically searched and analyzed the available evidence in order to evaluate the efficacy of polymyxins in the treatment of infections caused by CRE, and to examine whether polymyxin combination therapy can offer an advantage over monotherapy.

Methods

Search strategies

We searched the PubMed, Embase, and Cochrane Library databases from their inception until August 30, 2014 using the following search terms: (CRE or carbapenem-resistant or KPC or carbapenemase-producing or VIM or NDM or OXA or IMP) and (*Escherichia* or *Klebsiella* or *Enterobacter* or *Proteus* or *Serratia* or *Citrobacter* or *Salmonella* or *Shigella* or *Enterobacteriaceae*) and (colistin or polymyxin). The references listed in the identified studies were also searched to select relevant articles. No language restrictions were applied. The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement were used in the identified articles. Two investigators (Ni and Cai) independently performed the literature search and study selection. A third author (Wei) resolved any disagreements, and a final consensus was reached among all authors.

Selection criteria

Studies were considered eligible for inclusion if they provided clinical outcomes of polymyxin therapy for infections caused by carbapenemase-producing *Enterobacteriaceae* or CRE. For studies reporting the outcomes of both colonized and infected patients, only those of infected patients were extracted. Experimental trials in animals, trials focusing on pharmacokinetic or pharmacodynamic (PK/PD) variables, trials referring only to the *in vitro* activity of polymyxins, and incomplete unpublished studies were excluded. Case reports and case-series including fewer than 10 infected patients were also excluded.

Ethical considerations

This study did not require the approval of an ethics committee.

Data extraction and quality assessment

The following variables were collected from the included studies by two independent reviewers: author, publication year, country, study design, main characteristics and severity of illness (APACHE scores) of the study population, causative pathogens, antibiotic susceptibility testing methods and breakpoints, sites of infections, type and dose of polymyxin administered, coadministration of other antibiotics, outcomes (clinical response, microbiologic eradication, and mortality), and reported toxicity (nephrotoxicity and neurotoxicity).

The quality of the included studies was assessed using the modified Newcastle-Ottawa scale (NOS), which consists of three factors: patient selection, comparability of the study groups, and outcome assessment.[8] Studies with a NOS score <3 were classified as having poor quality and were excluded from this systematic review.

Definitions and statistical analysis

Because patients with CRE infections show high mortality rates, we chose mortality as the primary outcome. The secondary outcomes were clinical response, microbiologic eradication, and incidence of toxicity. Because of the lack of standard and uniform criteria for assessing and reporting these secondary outcomes, we accepted the criteria as reported in each study.

All statistical analyses were performed with the Comprehensive Meta-Analysis V2.2 (Biostat, Englewood NJ). The between-study heterogeneity was assessed by using χ^2-based Q statistics and the I^2 test. Heterogeneity was considered as $I^2 > 50\%$. Either fixed effects (Mantel–Haenszel method) or random effects (DerSimonian and Laird's method) models were used according to the heterogeneity result. Binary outcomes results of controlled studies were expressed as odds ratios (ORs). Egger regression and Begg and Mazumdar methods were used to evaluate publication bias, and $p < 0.05$ was considered statistically significant.

Results

A total of 1189 potentially relevant references were initially identified by searching the PubMed, Embase, and Cochrane Library databases (Fig. 1). Titles and abstracts were reviewed to exclude irrelevant studies. Two-hundred and thirty-two articles with full texts were screened, and 25 studies met the inclusion criteria.[9–33] The examination of the references of these included studies and review articles did not yield any further studies for evaluation. The NOS score of all included studies was >3.

Study characteristics

The characteristics of the included studies are presented in Table 1 . Among the 25 included studies, six involving 175 patients were single-arm studies, and 19 involving 911 patients were controlled studies. Two out of six single-arm studies were prospective studies, and the others were retrospective studies. Eight out of 19 controlled studies were prospective studies, and 11 were retrospective studies. Most patients in the included studies were critically ill. Twenty-two studies involving 881 patients reported that the proportion of patients in the intensive care unit was 64.6%. The average APACHE score of patients in 14 studies using this parameter was >20. Nine studies reported on CRE infections, and 16 other studies reported on carbapenemase-producing *Enterobacteriaceae* infections. *Klebsiella* spp. were the major causative pathogen, and bacteremia was the most common manifestation, followed by pneumonia and urinary tract infection.

Mortality

Among the 19 controlled studies, 18 involving 824 patients reported the mortality rate. As shown in Fig. 2, no significant difference in overall mortality was noted when the polymyxins-treated groups were compared with the control groups (OR, 0.79 [95% confidence interval (CI), 0.58–1.08; $p = 0.15$]; $I^2 = 0\%$; $Q = 15.12$ [$p = 0.59$]). The subgroup analysis of controlled studies is presented in Table 2.

For the six single-arm studies, the pooled overall mortality rate was 35.7% (95% CI, 0.22–0.53; $I^2 = 74.85\%$; $Q = 19.88$ [$p = 0.001$]), which was in line with the results of the controlled studies (33.8% [95% CI, 0.29–0.39]; $I^2 = 27.43\%$; $Q = 23.43$ [$p = 0.14$]).

The subgroup analysis by mortality type is shown in Table 3. With respect to 28-day or 30-day mortality, no significant difference was observed between the polymyxin monotherapy and control groups, while significantly lower mortality was noted in the combination therapy group. For other subgroup analyses, such as in-hospital mortality, 14-day mortality, and all-cause mortality, the rate did not differ significantly between the polymyxin-treated groups and the control groups. In addition, one study compared colistin with other antibiotics in terms of infection-related mortality, and no significant difference was found between the two groups.

No publication bias was detected by using Egger regression or Begg and Mazumdar rank correlation. Therefore, the funnel plot for publication bias demonstrated no marked evidence of asymmetry, as shown in Fig. 3.

Clinical response

Four studies involving 153 patients compared the clinical response of colistin-based therapy with that of other antibiotic regimens. As shown in Fig. 2, no significant difference was observed between the two groups (OR, 1.24 [95% CI, 0.61–2.54; $p = 0.55$]; $I^2 = 47.45\%$; $Q = 5.71$ [$p = 0.13$]). For the single-arm

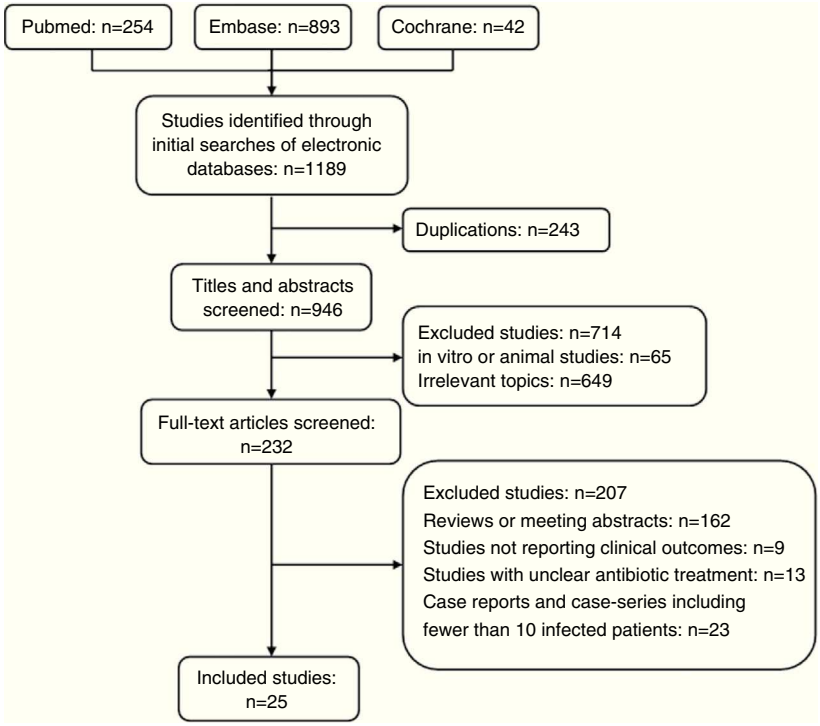

Fig. 1 – Flow chart of the articles selection process.

Table 1 – Characteristics of studies included in systematic review and meta-analysis.

Author (year)	Country and district	Type of study	Population characteristics	Polymyxin group	Concomitant antibiotics administered
Daikos (2009)[9]	Greece	Prospective, 2 arms	Inpatients	Colistin	Carba
Michalopoulos (2010)[10]	Greece	Prospective, 2 arms	ICU patients; DM, COPD; Mean APACHE score = 23.4 ± 4.9	Colistin	Fos
Nguyen (2010)[11]	United States	Retrospective, 2 arms	Inpatients (52.1% were ICU patients); Median APACHE score = 19 (range 12–35)	Polymyxin B	Tige
Souli (2010)[12]	Greece	Retrospective, 2 arms	Inpatients (64.7% were ICU patients); Mean APACHE score = 18.9 ± 7.4	Colistin	Carba, Tige, AG, FQ, Tzp
Satlin (2011)[13]	United States	Retrospective, 2 arms	2 were outpatients; 85 were Inpatients (15% were ICU patients)	Polymyxin B	None
Zarkotou (2011)[14]	Greece	Prospective, 2 arms	Inpatients (71.7% were in the ICU patients); Mean APACHE score = 21.1 ± 8.2	Colistin	Carba, Tige, AG
Alexander (2012)[15]	United States	Retrospective, 2 arms	Inpatients (21.4% were ICU patients)	Colistin	AG, Dox
Bergamasco (2012)[16]	Brazil	Retrospective, 2 arms	Solid-organ transplant recipients	Polymyxin B	Carba, Tige
Qureshi (2012)[17]	United States	Retrospective, 2 arms	Inpatients (52.9% were ICU patients at enrollment); 51.2% had an APACHE score ≥20	Colistin; Polymyxin B	Carba, Tige, FQ
Sanchez (2012)[18]	Spain	Retrospective, 2 arms	ICU patients; Mean APACHE scores = 21.5 ± 5.8	Colistin	Tige, AG
Tumbarello (2012)[19]	Italy	Retrospective, 2 arms	Inpatients (13.6% were in shock); Mean APACHE score >30	Colistin	Carba, Tige, AG
Capone (2013)[20]	Italy	Prospective, 2 arms	Inpatients (48.4% were ICU patients); Median APACHE score = 15 (range 12–20)	Colistin	Tige, AG, Fos
Navarro (2013)[21]	Spain	Prospective, 2 arms	Inpatients (23.5% were ICU patients); septic shock or severe sepsis (60%))	Colistin	Carba, Tige, AG, Fos
Balkan (2014)[22]	Turkey	Retrospective, 2 arms	Inpatients (58.8% were ICU patients)	Colistin	Carba, Tige, AG
Daikos (2014)[23]	Greece	Retrospective, 2 arms	Inpatients (56.6% were ICU patients)	Colistin	Carba, Tige, AG
Huang (2014)[24]	Taiwan	Retrospective, 2 arms	Inpatients (60.5% were ICU patients)	Colistin	None
Kontopidou (2014)[25]	Greece	Prospective, 2 arms	ICU patients; Mean APACHE score ≥20	Colistin	Carba, Tige, AG
Papadimitriou (2014)[26]	Greece	Prospective, 2 arms	ICU patients; Mean APACHE score = 16 ± 8.0	Colistin	Tige, AG
Pontikis (2014)[27]	Greece	Prospective, 2 arms	ICU patients, Mean APACHE scores = 18.13 ± 5.6	Colistin	Carba, Tige, AG, Tzp
Souli (2008)[28]	Greece	Retrospective, single arm	Inpatients (58.8% were ICU patients); Median APACHE score = 22 (range 10–33)	Colistin	Carba, AG, Tzp, FQ, Dox
Maltezou (2009)[29]	Greece	Retrospective, single arm	ICU patients	Colistin	Tige, AG
Mouloudi (2010)[30]	Greece	Retrospective, single arm	ICU patients	Colistin	AG
Di Carlo (2013)[31]	Italy	Prospective, single arm	ICU patients, Mean APACHE scores = 23.4 ±1.7	Colistin	Tige
Dubrovskaya (2013)[32]	United States	Retrospective, single arm	Inpatients (52.5% were ICU patients)	Colistin	None
Crusio (2014)[33]	Netherlands	Prospective, single arm	Inpatients; Mean APACHE scores = 20	Polymyxin B	Carba, A-S

Table 1 – (*Continued*)

Author (year)	Control group	Sample size (Polymyxin group/Control group)	Type of infection	Organisms isolated	Susceptibility testing method (susceptibility breakpoints used)	
					Polymyxins	Other antibiotics
Daikos (2009)[9]	Carba, AG	23/26	BSI	VIM-1-producing *Klebsiella pneumoniae*	Etest (CLSI, 2004)	Etest (CLSI, 2004)
Michalopoulos (2010)[10]	Fos, AG, Tzp	6/5	BSI, VAP, UTI, Wound infection	Carbapenem-resistant *K. pneumoniae*	NA	NA
Nguyen (2010)[11]	Tige, other	22/26	BSI	Carbapenem-resistant *K. pneumoniae*	Etest (CLSI, 2009)	Etest; Vitek 2 automated system (CLSI, 2009)
Souli (2010)[12]	Carba, Tige, AG, Tzp	14/3	BSI, SSI, UTI, HAP	KPC-producing *K. pneumoniae*	Etest (EUCAST, 2009)	Etest; Agar dilution (CLSI, 2009; FDA)
Satlin (2011)[13]	Tige, AG	25/62	UTI	Carbapenem-resistant *K. pneumoniae*	Etest (CLSI, 2011)	Etest; Vitek 2 automated system (CLSI, 2011; FDA)
Zarkotou (2011)[14]	Carba, Tige, AG	21/14	BSI	KPC-producing *K. pneumoniae*	Broth microdilution (EUCAST, 2010)	Vitek 2 automated system; Broth microdilution (CLSI, 2010)
Alexander (2012)[15]	AG, Dox, FQ, Ntf	2/12	UTI, BSI	KPC-producing *K. pneumoniae*	Disk diffusion (CLSI, 2006)	Disk diffusion; Etest (CLSI, 2006)
Bergamasco (2012)[16]	Carba, Tige	9/3	BSI, UTI, SSI, HAP	KPC-producing *K. pneumoniae*	Etest (CLSI, 2009)	Disk diffusion; Etest (CLSI, 2009; FDA)
Qureshi (2012)[17]	Carba, Tige, AG, FQ, Azt, Cfpm, Tzp, A-S	14/20	BSI	KPC-producing *K. pneumoniae*	Broth microdilution (CLSI, 2011)	Broth microdilution; Etest (CLSI, 2011)
Sanchez (2012)[18]	Carba, Tige, AG	12/12	Pneumonia, LRTI, UTI, Meningitis, BSI, IAI, SSTI	VIM-1-producing *K. pneumoniae*	Broth microdilution; Etest (CLSI, 2011)	Broth microdilution; Etest (CLSI, 2011; EUCAST, 2011)
Tumbarello (2012)[19]	Carba, Tige, AG	61/36	BSI	KPC-producing *K. pneumoniae*	Vitek 2 automated system (CLSI, 2011)	Vitek 2 automated system (CLSI, 2011; FDA)
Capone (2013)[20]	Tige, AG, Fos	36/22	BSI, UTI, Septic shock, LRTI, SSTI	KPC-producing *K. pneumoniae*	Broth microdilution (EUCAST, 2010)	Broth microdilution (EUCAST, 2010)
Navarro (2013)[21]	Carba, Tige, AG, Fos, FQ, Cef	18/16	BSI	OXA-48-producing *Enterobacteriaceae* (*K. pneumoniae*, *Escherichia coli*)	Etest (CLSI, 2012)	Vitek 2 automated system; Etest (CLSI, 2012; FDA)
Balkan (2014)[22]	Carba, Tige, AG	24/12	BSI	OXA-48-producing *Enterobacteriaceae* (*K. pneumoniae*, *E. coli*, *Enterobacter aerogenes*)	Etest (EUCAST, 2013)	Etest (EUCAST, 2013)

Daikos (2014)[23]	Carba, Tige, AG, other	78/86	BSI	Carbapenem-Resistant *K. pneumoniae*	Etest (EUCAST, 2013)	Etest; Vitek 2 automated system (EUCAST, 2013)
Huang (2014)[24]	Carba, Tige	4/29	NA	Carbapenem-resistant *Enterobacteriaceae* (*K. pneumoniae*, *E. coli*)	Broth microdilution (EUCAST, 2012)	Broth microdilution (EUCAST, 2012)
Kontopidou (2014)[25]	Tige, AG, FQ	57/50	VAP, UTI, BSI, SSI, IAI	Carbapenem-Resistant *K. pneumoniae*	Vitek 2 automated system (EUCAST, 2012)	Etest; Vitek 2 automated system (CLSI, 2010; EUCAST, 2012)
Papadimitriou (2014)[26]	Tige, AG	19/17	BSI	KPC-producing *K. pneumoniae*	Etest (CLSI, 2011)	Etest, Disk diffusion (CLSI, 2011)
Pontikis (2014)[27]	Tige, AG	10/5	BSI, UTI, VAP, IAI, Meningitis	Carbapenem-Resistant *K. pneumoniae*	Vitek 2 automated system (CLSI, 2012)	Vitek 2 automated system (CLSI, 2012; FDA)
Souli (2008)[28]	NA	16/NA	BSI; VAP	VIM-1, MBL producing *Enterobacteriaceae* (*Klebsiella spp.*, *Enterobacter spp.*)	Etest (BSAC)	Disk; Etest (CLSI, 2006)
Maltezou (2009)[29]	NA	11/NA	Pneumonia, SSI	KPC-2-producing *K. pneumoniae*	Etest (CLSI, 2007)	Disk; Etest (CLSI, 2007)
Mouloudi (2010)[30]	NA	53/NA	BSI	KPC, MBL producing *K. pneumoniae*	Etest (EUCAST, 2010)	Etest, Broth microdilution (CLSI, 2007; FDA)
Di Carlo (2013)[31]	NA	30/NA	SSI, IAI,	KPC-producing *K. pneumoniae*	Etest (EUCAST, 2013)	Broth microdilution (EUCAST, 2013)
Dubrovskaya (2013)[32]	NA	40/NA	BSI, UTI, SSI, Pneumonia, IAI	Carbapenem-Resistant *K. pneumoniae*	Etest (CLSI, 2012)	Etest; Vitek 2 automated system (CLSI, 2012; FDA)
Crusio (2014)[33]	NA	25/NA	BSI, VAP, UTI	Carbapenem-Resistant *K. pneumoniae*	Vitek 2 automated system (CLSI, 2009)	Vitek 2 automated system (CLSI, 2009)

Abbreviation: NA, not applicable; ICU, intensive care unit; BSI, bloodstream infection; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; SSI, surgical-site infection; HAP, hospital-acquired pneumonia; LRTI, lower respiratory tract infection; IAI, intra-abdominal infection; SSTI, skin and soft tissue infection. Carba, carbapenem; Tige, tigecycline; Ntf, nitrocefin; Fos, fosfomycin; AG, aminoglycoside; A-S, ampicillin-sulbactam; Azt, aztreonam; FQ, fluoroquinolone; Caz, ceftazidime; Cfpm, cefepime; Cef, Ceftriaxone; Tzp, piperacillin-tazobactam; Dox, doxycycline; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration; BSAC, British Society for Antimicrobial Chemotherapy.

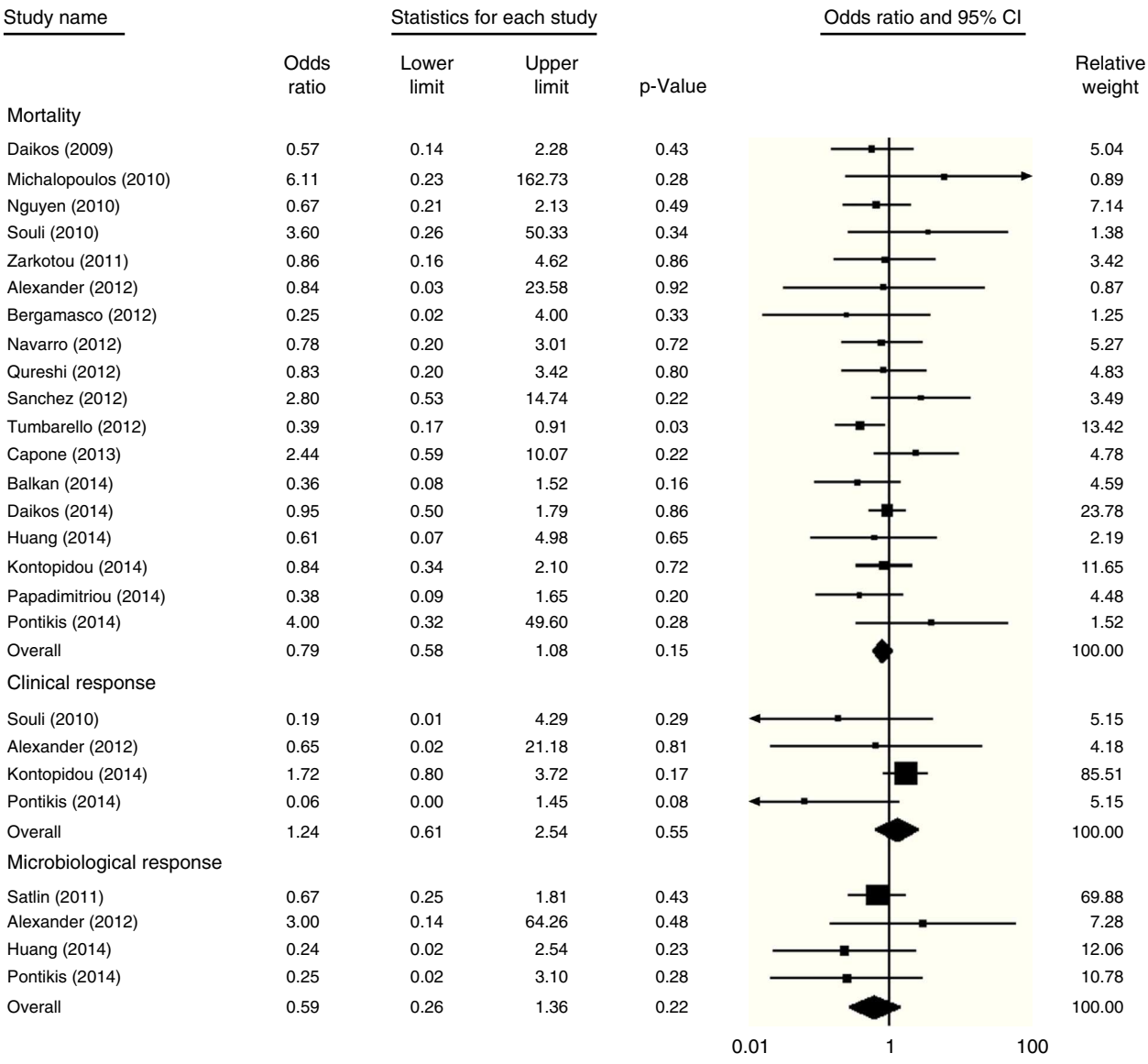

Fig. 2 – The efficacy of polymyxins compared with other antibiotics in treating infections caused by carbapenemase-producing *Enterobacteriaceae* and carbapenem-resistant *Enterobacteriaceae*.

studies (three studies; 81 patients), the favorable clinical response was 75% (95% CI, 0.64–0.83; $I^2 = 0\%$; Q = 1.50 [$p = 0.47$]). One study compared colistin combination therapy (13 of 31 patients) with monotherapy (8 of 26 patients), and no significant difference was found between the two groups ($p = 0.55$).

Microbiological response

As shown in Fig. 2, four studies involving 149 patients reported the outcome of microbiological response. No significant difference was noted between the polymyxin-treated groups and the control groups (OR, 0.59 [95% CI, 0.26–1.36; $p = 0.22$]; $I^2 = 0\%$; Q = 2.17 [$p = 0.54$]). In three single-arm studies (62 patients), the overall microbiological response rate was 51% (95% CI, 0.38–0.63; $I^2 = 28.30\%$; Q = 2.79 [$p = 0.25$]).

Adverse events

Neurotoxicity was not reported in any of the studies. Only one controlled study and two single-arm studies evaluated the occurrence of nephrotoxicity. Pooled analysis showed an incidence rate of 19.2% (95% CI, 0.08–0.39; $I^2 = 67.12\%$; Q = 6.08 [$p = 0.05$]).

Discussion

Carbapenemase-producing *Enterobacteriaceae*, particularly KPC-producing *K. pneumoniae*, is now widespread and endemic in many countries.[34] Infections caused by these MDR organisms are associated with high treatment failure and mortality.[35] However, available effective therapeutic options are scarce. In this situation, polymyxins, which exhibit potent *in vitro* activity against MDR Gram-negative

Table 2 – Subgroup analysis of overall mortality with polymyxin-based therapy *versus* control antibiotics for treatment of carbapenem-producing *Enterobacteriaceae* and carbapenem-resistant *Enterobacteriaceae* infections in controlled studies.

Variables	Studies, no. (patients, no.)	Comparison of mortality between polymyxins and control OR (95% CI); *P*	Heterogeneity of studies included
Carbapenem-resistant *K. pneumoniae*	10 (414)	0.71 (0.48–1.05); $p = 0.09$	$I^2 = 0\%$; Q = 8.98; $p = 0.53$
Bloodstream infection	12 (551)	0.75 (0.52–1.08); $p = 0.12$	$I^2 = 0\%$; Q = 10.04; $p = 0.53$
By study design			
Prospective	8 (345)	0.92 (0.55–1.54); $p = 0.76$	$I^2 = 0\%$; Q = 6.34; $p = 0.50$
Retrospective	12 (491)	0.70 (0.48–1.03); $p = 0.07$	$I^2 = 0\%$; Q = 9.81; $p = 0.55$
By concomitant antibiotics			
Polymyxin alone	12 (133)	1.24 (0.80–1.93); $p = 0.33$	$I^2 = 0\%$; Q = 8.83; $p = 0.64$
Polymyxin + carbapenem	7 (35)	0.84 (0.33–2.13); $p = 0.71$	$I^2 = 0\%$; Q = 3.48; $p = 0.72$
Polymyxin + tigecycline	13 (118)	0.81 (0.50–1.33); $p = 0.41$	$I^2 = 12.50\%$; Q = 13.71; $p = 0.32$
Polymyxin + aminoglycoside	9 (78)	0.91 (0.50–1.63); $p = 0.75$	$I^2 = 5.63\%$; Q = 8.47; $p = 0.38$
Polymyxin + ≥2 antibiotics	11 (72)	0.51 (0.27–0.97); $p = 0.04$	$I^2 = 18.26\%$; Q = 12.23; $p = 0.27$

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3 – Subgroup analysis of mortality with different polymyxin treatment strategies in the treatment of carbapenem-producing *Enterobacteriaceae* and carbapenem-resistant *Enterobacteriaceae* infections.

Mortality	Studies, no. (patients, no.)	Comparison of mortality between different treatment strategies OR (95% CI); *P*	Heterogeneity of studies included
By 28-day or 30-day			
Monotherapy-Control	8 (303)	1.15 (0.66–2.01); $P = 0.60$	$I^2 = 0\%$; Q = 4.17; $P = 0.76$
Combination-Control	9 (410)	0.49 (0.31–0.75); $P < 0.01$	$I^2 = 0\%$; Q = 7.15; $P = 0.52$
Combination-Monotherapy	7 (221)	0.36 (0.19–0.68); $P < 0.01$	$I^2 = 0\%$; Q = 3.29; $P = 0.77$
By 14-day			
Monotherapy-Control	2 (122)	0.84 (0.35–2.00); $P = 0.69$	$I^2 = 0\%$; Q = 0.08; $P = 0.78$
Combination-Control	2 (110)	0.76 (0.27–2.16); $P = 0.60$	$I^2 = 21.20\%$; Q = 1.27; $P = 0.26$
Combination-Monotherapy	2 (80)	0.91 (0.28–2.96); $P = 0.88$	$I^2 = 36.47\%$; Q = 1.57; $P = 0.21$
By In hospital			
Combination-Control	3 (73)	2.01 (0.56–7.20); $P = 0.28$	$I^2 = 0\%$; Q = 0.71; $P = 0.70$
Combination-Monotherapy	2 (89)	0.97 (0.38–2.46); $P = 0.95$	$I^2 = 31.08\%$; Q = 1.45; $P = 0.23$
By All-cause			
Combination-Control	2 (41)	3.00 (0.74–12.26); $P = 0.125$	$I^2 = 0\%$; Q = 0.02; $P = 0.87$

Abbreviations: OR, odds ratio; CI, confidence interval.

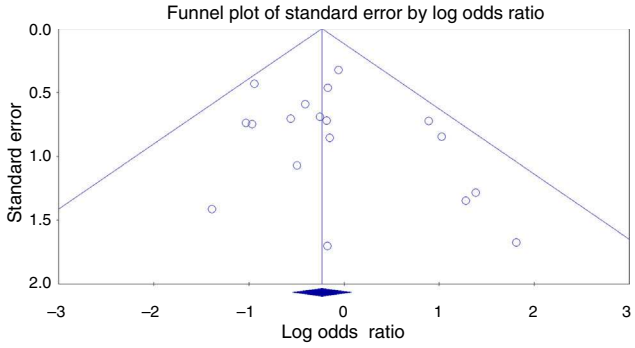

Fig. 3 – A funnel plot of mortality rate in patients treated with polymyxins compared with that in patients treated with other antibiotics for infections caused by carbapenemase-producing *Enterobacteriaceae* and carbapenem-resistant *Enterobacteriaceae*.

bacteria, have recently become the focus of interest to clinicians.[36] Nevertheless, before polymyxins were widely reintroduced in the clinic, comprehensive and objective evaluation of these "old antibiotics" was of great necessity.

In this systemic review, we assessed the available evidence for the efficacy of polymyxins in treating CRE infections. Although no statistical difference was observed, a strong tendency toward lower mortality was noted in the polymyxin-treated groups (OR, 0.79; 95% CI, 0.58–1.08). As for the clinical and microbiological response, pooled data showed no significant difference between the two groups. Therefore, we can at least conclude that polymyxins are as efficacious as other antibiotics for treating CRE infections.

Nevertheless, the rapid emergence of resistant isolates and suboptimal pharmacokinetics may challenge the efficacy of polymyxins in treating MDR infections, especially bacteremia and pneumonia.[37,38] Many clinicians believe that combination therapy may overcome these shortcomings. Prospective studies showed that polymyxin-based combination therapy

could result in better clinical and microbiological outcomes than monotherapy, but failed to provide evidence for the superiority of combination therapy in lowering mortality when treating MDR *Acinetobacter baumannii* infections.[39–41] The role of combination therapy in CRE infections has not been well evaluated. In the subgroup analyses of our study, polymyxin monotherapy did not lower the 28-day or 30-day mortality, and the outcome was in favor of the control groups. In contrast, combination therapy significantly lowered the 28-day or 30-day mortality. This indicates that polymyxin combination therapy may have an advantage over monotherapy in treating CRE infections, although the evidence is not strong enough.

Several important questions regarding combination therapy remain unanswered, such as the best combination for each infection type, the continued role for carbapenems in combination therapy, and the timing of combination therapy initiation.[7] A number of *in vitro* synergy tests have been performed to verify the synergistic effects of polymyxins in combination with other antibiotics.[42–44] However, the significant synergy observed *in vitro* should be carefully interpreted, because the PK/PD effects of drugs *in vivo*, bacterial load, and drug concentrations in specific sites of infection are different.[45] A recent study found that when the minimum inhibitory concentrations (MICs) for carbapenems were ≤8 mg/L, carbapenem-containing regimens seemed to offer therapeutic advantage over other regimens.[46] However, for *Enterobacteriaceae* with MICs for carbapenems >8 mg/L, a combination of two or even three antibiotics, such as colistin, high-dose tigecycline, aminoglycoside, and fosfomycin, seemed to decrease mortality.[46] In this study, subgroup analyses revealed that polymyxins combined with carbapenems, tigecycline, or aminoglycosides could not significantly lower mortality; only triple polymyxin-containing combinations seemed to do so. Considering the limited number of patients and potential bias existing in the included studies, we cannot draw definitive conclusions. Much research is needed in the future to address these significant questions.

The biggest limitation to the wider clinical application of polymyxins is the dosing-related nephrotoxicity and neurotoxicity. Among the included studies, only one controlled study and two single-arm studies evaluated the occurrence of nephrotoxicity, and pooled analysis showed an incidence rate of 19.2%. No studies have reported any incidences of neurotoxicity, such as seizures, encephalopathy, and neuromuscular blockade. Owing to the limited available data, we were unable to compare the safety between the polymyxin-treated groups and the control groups. Recent studies report less frequent and severe adverse effects than that reported in the 1970s.[47] Other published systemic reviews have concluded that the administration of polymyxins was not associated with a relatively higher incidence of nephrotoxicity.[36,41] Possible reasons might be improved purified drug formulations, careful dosing, close renal function monitoring, and more advanced critical care services.[38] However, renal function should always be closely monitored during administration, and the clinical safety of polymyxins requires further investigation.

Our study should be interpreted with caution, as it has limitations that must be taken into account. The main limitation is that none of the included studies were prospective randomized controlled trials (RCTs). Therefore, we were unable to control for some confounding factors such as different patient populations, different sites of infections, different genotypes of pathogens, and different antimicrobial susceptibility breakpoints. Another limitation is that most of the included studies did not provide sufficient detail to facilitate the comprehensive interpretation of the results, such as the MICs, total daily doses, time to initiate therapy, and duration of therapy. In addition, the sample size for specific subgroup analysis was small, which may reduce the power of statistical analyses.

In summary, this systematic review and meta-analysis indicates that polymyxins and other antimicrobial therapies may have similar efficacy in the treatment of infections caused by carbapenemase-producing *Enterobacteriaceae* and CRE. Compared with polymyxin monotherapy, combination regimens may achieve lower 28-day or 30-day mortality. However, the inherent limitations of the included studies prevent us from reaching definitive conclusions. Future large-volume, well-designed RCTs are required to determine the role of polymyxins in treating CRE infections.

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Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. van Duin D, Kaye KS, Neuner EA, Bonomo RA. Carbapenem-resistant *Enterobacteriaceae*: a review of treatment and outcomes. Diagn Microbiol Infect Dis. 2013;75:115–20.
2. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Lancet Infect Dis. 2009;9:228–36.
3. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumonia* and other *Enterobacteriaceae*: an evolving crisis of global dimensions. Clin Microbiol Rev. 2012;25:682–707.
4. Livermore DM, Warner M, Mushtaq S, Doumith M, Zhang J, Woodford N. What remains against carbapenem-resistant *Enterobacteriaceae?* Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. Int J Antimicrob Agents. 2011;37:415–9.
5. Biswas S, Brunel JM, Dubus JC, Reynaud-Gaubert M, Rolain JM. Colistin: an update on the antibiotic of the 21st century. Expert Rev Anti Infect Ther. 2012;10:917–34.
6. Lee GC, Burgess DS. Treatment of *Klebsiella pneumoniae* carbapenemase (KPC) infections: a review of published case series and case reports. Ann Clin Microbiol Antimicrob. 2012;11:32.
7. Petrosillo N, Giannella M, Lewis R, Viale P. Treatment of carbapenem-resistant *Klebsiella pneumoniae*: the state of the art. Expert Rev Anti Infect Ther. 2013;11:159–77.

8. Wells GA. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses; 2015, available: http://www.ohri.ca/programs/clinicalepidemiology/oxford.asp [accessed 10.11.13].
9. Daikos GL, Petrikkos P, Psichogiou M, et al. Prospective observational study of the impact of VIM-1 metallo-(beta)-lactamase on the outcome of patients with *Kebsiella pneumoniae* bloodstream infections. Antimicrob Agents Chemother. 2009;53:1868–73.
10. Michalopoulos A, Virtzili S, Rafailidis P, Chalevelakis G, Damala M, Falagas ME. Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation. Clin Microbiol Infect. 2010;16:184–6.
11. Nguyen M, Eschenauer GA, Bryan M, et al. Carbapenem-resistant *Klebsiella pneumoniae* bacteremia: factors correlated with clinical and microbiologic outcomes. Diagn Microbiol Infect Dis. 2010;67:180–4.
12. Souli M, Galani I, Antoniadou A, et al. An outbreak of infection due to beta-Lactamase *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* in a Greek University Hospital: molecular characterization, epidemiology, and outcomes. Clin Infect Dis. 2010;50:364–73.
13. Satlin MJ, Kubin CJ, Blumenthal JS, et al. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem-resistant *Klebsiella pneumoniae* from urine. Antimicrob Agents Chemother. 2011;55:5893–9.
14. 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. Clin Microbiol Infect. 2011;17:1798–803.
15. Alexander BT, Marschall J, Tibbetts RJ, Neuner EA, Dunne WM Jr, Ritchie DJ. Treatment and clinical outcomes of urinary tract infections caused by KPC-Producing *Enterobacteriaceae* in a retrospective cohort. Clin Ther. 2012;34:1314–23.
16. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, et al. Infection with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in solid organ transplantation. Transpl Infect Dis. 2012;14:198–205.
17. Qureshi ZA, Paterson DL, Potoski BA, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother. 2012;56:2108–13.
18. Sanchez-Romero I, Asensio A, Oteo J, et al. Nosocomial outbreak of VIM-1-producing *Klebsiella pneumoniae* isolates of multilocus sequence type 15: molecular basis, clinical risk factors, and outcome. Antimicrob Agents Chemother. 2012;56:420–7.
19. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. Clin Infect Dis. 2012;55:943–50.
20. Capone A, Giannella M, Fortini D, et al. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. Clin Microbiol Infect. 2013;19:E23–30.
21. Navarro-San Francisco C, Mora-Rillo M, Romero-Gómez MP, et al. Bacteraemia due to OXA-48-carbapenemase-producing *Enterobacteriaceae*: a major clinical challenge. Clin Microbiol Infect. 2013;19:E72–9.
22. Balkan II, Aygün G, Aydın S, et al. Blood stream infections due to OXA-48-like carbapenemase-producing *Enterobacteriaceae*: treatment and survival. Int J Infect Dis. 2014;26:51–6.
23. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother. 2014;58:2322–8.
24. Huang SR, Liu MF, Lin CF, Shi ZY. Molecular surveillance and clinical outcomes of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* infections. J Microbiol Immunol Infect. 2014;47:187–96.
25. Kontopidou F, Giamarellou H, Katerelos P, et al. Infections caused by carbapenem-resistant *Klebsiella pneumoniae* among patients in intensive care units in Greece: a multi-centre study on clinical outcome and therapeutic options. Clin Microbiol Infect. 2014;20:O117–23.
26. Papadimitriou-Olivgeris M, Marangos M, Christofidou M, et al. Risk factors for infection and predictors of mortality among patients with KPC-producing *Klebsiella pneumoniae* bloodstream infections in the intensive care unit. Scand J Infect Dis. 2014;46:642–8.
27. Pontikis K, Karaiskos I, Bastani S, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents. 2014;43:52–9.
28. Souli M, Kontopidou FV, Papadomichelakis E, Galani I, Armaganidis A, Giamarellou H. Clinical experience of serious infections caused by *Enterobacteriaceae* producing VIM-1 metallo-beta-lactamase in a Greek University Hospital. Clin Infect Dis. 2008;46:847–54.
29. Maltezou HC, Giakkoupi P, Maragos A, et al. Outbreak of infections due to KPC-2-producing *Klebsiella pneumoniae* in a hospital in Crete (Greece). J Infect. 2009;58:213–9.
30. Mouloudi E, Protonotariou E, Zagorianou A, et al. Bloodstream infections caused by metallo-β-lactamase/*Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes. Infect Control Hosp Epidemiol. 2010;31:1250–6.
31. Di Carlo P, Gulotta G, Casuccio A, et al. KPC-3 *Klebsiella pneumoniae* ST258 clone infection in postoperative abdominal surgery patients in an intensive care setting: analysis of a case series of 30 patients. BMC Anesthesiol. 2013;13:13.
32. Dubrovskaya Y, Chen TY, Scipione MR, et al. Risk factors for treatment failure of polymyxin B monotherapy for carbapenem-resistant *Klebsiella pneumoniae* infections. Antimicrob Agents Chemother. 2013;57:5394–7.
33. Crusio R, Rao S, Changawala N, et al. Epidemiology and outcome of infections with carbapenem-resistant Gram-negative bacteria treated with polymyxin B-based combination therapy. Scand J Infect Dis. 2014;46:1–8.
34. Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 2001;45:1151–61.
35. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumonia* in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med. 2005;165:1430–5.
36. Florescu DF, Qiu F, McCartan MA, Mindru C, Fey PD, Kalil AC. What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. Clin Infect Dis. 2012;54:670–80.
37. Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother. 2012;67:1607–15.
38. Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed

colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother. 2011;55:3284–94.
39. 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. Clin Infect Dis. 2013;57:349–58.
40. Sirijatuphat R, Thamlikitkul V. Colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections: a preliminary study. Antimicrob Agents Chemother. 2014;58:5598–601.
41. Liu Q, Li W, Feng Y, Tao C. Efficacy and safety of polymyxins for the treatment of *Acinectobacter baumannii* infection: a systematic review and meta-analysis. PLOS ONE. 2014;9:e98091.
42. Pankey GA, Ashcraft DS. Detection of synergy using the combination of polymyxin B with either meropenem or rifampin against carbapenemase-producing *Klebsiella pneumoniae*. Diagn Microbiol Infect Dis. 2011;70:561–4.
43. Deris ZZ, Yu HH, Davis K, et al. The combination of colistin and doripenem is synergistic against *Klebsiella pneumonia* at multiple inocula and suppresses colistin resistance in an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother. 2012;56:5103–12.
44. Jernigan MG, Press EG, Nguyen MH, Clancy CJ, Shields RK. The combination of doripenem and colistin is bactericidal and synergistic against colistin-resistant, carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 2012;56:3395–8.
45. Zusman O, Avni T, Leibovici L, et al. Systematic review and meta-analysis of in vitro synergy of polymyxins and carbapenems. Antimicrob Agents Chemother. 2013;57:5104–11.
46. Rafailidis PI, Falagas ME. Options for treating carbapenem-resistant *Enterobacteriaceae*. Curr Opin Infect Dis. 2014;27:479–83.
47. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis. 2005;40:1333–41.