

Intravenous colistin combination is superior to monotherapy against carbapenem-resistant gram-negative bacterial infections: evidence from seven randomized controlled trials

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Abstract

Background Previous meta-analysis based on five randomized controlled trials (RCTs) did not display that intravenous colistin-based combination therapy is more efficacious than monotherapy against carbapenem resistant gram-negative bacterial infections. This meta-analysis aimed to further elucidate the efficacy.

Methods PubMed, Embase, and Cochrane databases were searched up to March 2019 and only RCTs evaluating the combination therapy versus monotherapy against carbapenem or even colistin-resistant gram-negative bacteria infections were included. RevMan 5.3 was used to perform meta-analysis.

Results Seven RCTs involving 859 patients were included. Total analysis showed that the combination therapy had a trend towards higher microbial response (RR, 1.21; 95% CI, 0.98 – 1.51), lower infection-related mortality (RR, 0.75; 95% CI, 0.53–1.05), and significantly lower nephrotoxicity (RR, 0.77; 95% CI, 0.60 – 0.98) than monotherapy. Subgroup analysis on carbapenem-resistant *A. baumannii* infections displayed that the combination therapy had significantly higher microbiological response (RR, 1.39; $P < 0.001$; 95% CI, 1.19–1.61). Another subgroup analysis on combination regimen for colistin plus rifampicin showed that the combination therapy had significantly higher eradication rate to carbapenem-resistant *A. baumannii* (RR, 1.35; 95% CI, 1.08–1.68). However, total and subgroup analysis showed no significant difference in all-cause mortality.

Conclusions The present study suggests that intravenous colistin-based combination regimen, especially colistin plus rifampicin, may be superior to colistin alone against gram-negative bacterial infections, especially *A. baumannii* infection

Background

With the current emergence of carbapenem-resistant gram-negative bacteria including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* worldwide [1–3] and the severe shortage of new active antimicrobial agents, intravenous polymyxins including colistin and polymyxin B—which were abandoned due to high incidence of nephrotoxicity in the early 1970s[4], are now reconsidered as an effective treatment [5–9]. However, polymyxins-resistant gram-negative bacteria, which are also resistant to carbapenem, have occasionally emerged [3, 10]. These carbapenem-resistant gram-negative bacteria have not only posed an urgent threat to global public health, but also become an immense challenge for clinical therapy [11–14].

To solve the above therapeutic problems, some respective or retrospective studies compared the effectiveness and nephrotoxicity of intravenous colistin-based combination therapy and high dose colistin monotherapy [15–17]. However, these clinical studies did not show consistent results on the effectiveness. To resolve these inconsistent findings, four meta-analyses were performed by Zusman et al. in 2017 [18], Vardakaset et al. in 2018 [19], Wang et al. in 2018 [20] and Cheng et al. in 2018 [21], respectively. But only the meta-analysis conducted by Cheng et al. [21] provided higher quality evidence based on five prospective randomized controlled trials (RCTs [22–26]) to find that intravenous colistin-based combination therapy was not superior to monotherapy. Recently, two additional RCTs [27, 28] compared the effects of intravenous colistin combination therapy and monotherapy on carbapenem- and colistin-resistant gram-negative bacteria infections. Therefore, the present meta-analysis was conducted based on seven RCTs further to provide higher quality evidence to elucidate whether intravenous colistin combination therapy is better than monotherapy against carbapenem-resistant gram-negative bacterial infections.

Methods

This meta-analysis was performed in accordance with the PRISMA-P (preferred reporting items for systematic reviews and meta-analysis protocols) statement which is recommended for the establishment of a systematic review and meta-

analysis [29].

Focused question

Is intravenous colistin-based Combination therapy more efficacious than monotherapy in the treatment of carbapenem-resistant gram-negative bacteria infections?

Inclusion and exclusion criteria

Publications that were not restricted by language were included. The inclusion criteria in the present meta-analysis were as follows: (1) RCTs; (2) the clinical effectiveness and nephrotoxicity of colistin-based combination antimicrobial therapy and colistin monotherapy were compared in the treatment of carbapenem- and colistin- gram-negative bacteria infections in adult patients; (3) colistin or polymyxin B was administered intravenously. Studies were excluded if they did not meet each of these inclusion criteria.

Search strategies

All clinical studies were identified by a systematic review of the literature from the PubMed, Embase, and Cochrane databases up to March 2019 using the following search terms: "colistin or polymyxin," "gram negative bacteria or *Acinetobacter baumannii* or *Enterobacteriaceae* or *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*," and "prospective or randomized." In addition, the reference lists of the selected manuscripts and related reviews were also screened manually to determine whether additional publications were available. The search strategies used are shown as follow.

1) PubMed

("colistin" [MeSH Terms] OR "colistin" [All Fields]) OR ("polymyxins" [MeSH Terms] OR "polymyxins" [All Fields] OR "polymyxin" [All Fields]) AND (("gram negative bacteria" [All Fields] OR "gram-negative bacteria" [MeSH Terms] OR ("gram-negative" [All Fields] AND "bacteria" [All Fields]) OR "gram-negative bacteria" [All Fields] OR ("gram" [All Fields] AND "negative" [All Fields] AND "bacteria" [All Fields]) OR "gram negative bacteria" [All Fields]) OR ("*Acinetobacter baumannii*" [MeSH Terms] OR ("*Acinetobacter*" [All Fields] AND "*baumannii*" [All Fields]) OR "*Acinetobacter baumannii*" [All Fields]) OR ("*Klebsiella pneumoniae*" [MeSH Terms] OR ("*Klebsiella*" [All Fields] AND "*pneumoniae*" [All Fields]) OR "*Klebsiella pneumoniae*" [All Fields]) OR ("*Pseudomonas aeruginosa*" [MeSH Terms] OR ("*Pseudomonas*" [All Fields] AND "*aeruginosa*" [All Fields]) OR "*Pseudomonas aeruginosa*" [All Fields]) OR ("*Enterobacteriaceae*" [MeSH Terms] OR "*Enterobacteriaceae*" [All Fields]) AND ("longitudinal studies" [MeSH Terms] OR ("longitudinal" [All Fields] AND "studies" [All Fields]) OR "longitudinal studies" [All Fields] OR "prospective" [All Fields]) OR ("random allocation" [MeSH Terms] OR ("random" [All Fields] AND "allocation" [All Fields]) OR "random allocation" [All Fields] OR "randomized" [All Fields]) OR randomized [All Fields]).

2) Embase.

(1) colistin OR polymyxin;

(2) gram negative bacteria OR *Acinetobacter baumannii* OR *Klebsiella pneumonia* OR *Pseudomonas aeruginosa* OR *Enterobacteriaceae*;

(3) randomized OR prospective;

(4) (1) AND (2) AND (3).

3) Cochrane databases.

- (1) MeSH descriptor colistin explode all trees;
- (2) MeSH descriptor polymyxin explode all trees;
- (3) (1) OR (2).

Study selection and data extraction

During study selection, duplicate studies or datasets were firstly removed from the included titles using EndNote software. The titles and summaries of the rest of studies were then sifted through, followed by full-text screening according to the inclusion criteria described above (Figure 1). The results were independently screened by two authors, and a third author was consulted if any discrepancies occurred.

The following data, including the year of publication, the place of study, the type of infection, bacteria, the dosage of colistin including loading dose and combined antimicrobial regimens, microbiological outcomes, infection-related mortality, all-cause mortality and nephrotoxicity, were extracted from each included study.

Quality assessment

Cochrane risk of bias assessment tool was used to evaluate the quality of enrolled RCTs and the risk of bias [30]. The risks of bias include random sequence generation (selection bias), assignment concealment (selection bias), blinding of participants and personnel (performance bias), blind assessment of outcome (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases. These bias risks contained three levels: low, unclear and high (Figure 2).

Definitions and outcomes

The main outcome was microbial response or microbial eradication because this index can really reflect the effectiveness of antimicrobial drugs. Secondary outcomes included all-cause or crude mortality at any timeframe, which mainly referred to 28- or 30-day incidence, infection-related mortality, and nephrotoxicity. The mean/median colistin dose or the administered dose of more than 6 million international units (MIU) was defined as high dose of colistin, as mentioned earlier [21].

Statistical analysis

Review Manager Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to perform the statistical analysis. The between-study heterogeneity was evaluated by Q test and I^2 , Where the P -value was less than 0.05 and I^2 was more than 50%, heterogeneity was defined as significant and the Mantel–Haenszel random effects model was used. Otherwise, the fixed-effects model was used.

The pooled risk ratio (RR) and 95% confidence interval (CI) were calculated for result analysis. Sensitivity analyses were performed by the sequential omission of each study.

Ethics

Ethical approval was not required for such types of research articles.

Results

Study selection and characteristics

A total of 7 RCTs that met the inclusion criteria were included in this meta-analysis (Figure 1). Six out of seven studies included were open label, and except one bias, the blinding of participants and personnel (performance bias), most of the biases were classified as low or unclear risk of bias (Figure 2 and Figure 3).

The total number of patients included was 859 and mean age of these patients ranged from 56.2 to 76.0 years according to mean age provided by 7 RCTs papers.

Pneumonia, including ventilator-associated pneumonia and hospital-acquired pneumonia, was primary Infection type, and bloodstream infection was the next (Table 1). Carbapenem-resistant *A. baumannii* presented in the studies by Aydemir et al. [22], Makirs et al. [25], and Sirijatuphat et al. [24], extensive-drug including carbapenem resistant *A. baumannii* in the study by Durante-Mangoni et al. [23], Colistin-resistant *A. baumannii* in the study by Park et al. [28], carbapenem-resistant *K. pneumoniae* in the study by Abdelsalam et al. [27], and carbapenem-resistant gram-negative bacteria, including *A. baumannii*, *Enterobacteriaceae*, *Pseudomonas*, and others, in the study by Paul et al. [26]. There are 25.0% patients who complicated chronic kidney diseases.

All included studies designed intravenous colistin monotherapy and colistin-based combination regimens, the latter of which included colistin plus rifampicin [22, 23, 28], fosfomycin [24], meropenem [26, 27], or ampicillin-sulbactam [25]. Five studies [22, 24–27] adopted a high dose of colistin, among which two studies [26, 27] used a loading dose of colistin, one study [23] used a low dose of colistin, and another study [28] did not report the dose of colistin.

Six studies [22–27] reported the outcome of microbial response, seven [22–28] reported the outcome of crude mortality, four [22–25] reported the outcome of infection-related mortality, and four [23, 24, 26, 28] reported the outcome of nephrotoxicity (Table 2).

Meta-analysis results

1) Microbiological response

Intravenous colistin-based combination therapy showed a trend towards significantly higher microbiological response (RR, 1.21; $P = 0.08$; 95% CI, 0.98–1.51; $I^2 = 68\%$; Figure 4a). Subgroup analysis on carbapenem-resistant *A. baumannii* infections displayed that colistin-based combination therapy had significantly higher microbiological response (RR, 1.39; $P < 0.001$; 95% CI, 1.19–1.61; $I^2 = 45\%$; Figure 4b). Subgroup analysis on combination regimen for colistin plus rifampicin also displayed that colistin-based combination therapy had significantly higher eradication rate to carbapenem-resistant *A. baumannii* infections (RR, 1.35; $P = 0.008$; 95% CI, 1.08–1.68; $I^2 = 0\%$; Figure 4c).

2) All-cause mortality.

All-cause mortality was not significantly different between patients receiving intravenous colistin-based combination therapy and those receiving monotherapy (RR, 0.96; $P = 0.57$; 95% CI, 0.83–1.11; $I^2 = 12\%$; Figure 5a). Sensitivity analysis showed similar findings by the sequential omission of each study. Subgroup analysis on carbapenem-resistant *A. baumannii* infections displayed that colistin-based combination therapy was also not associated with lower all-cause mortality than monotherapy (RR, 1.08; $P = 0.58$; 95% CI, 0.83–1.40; $I^2 = 52\%$; Figure 5b). Subgroup analysis on combination regimen for colistin plus rifampicin displayed that colistin-based combination therapy was not associated with lower all-cause mortality than monotherapy (RR, 0.98; $P = 0.86$; 95% CI, 0.76–1.26; $I^2 = 0\%$; Figure 5c).

3) Infection-related mortality

Four studies [22–25] (Table 2) reported the results of infection-related mortality, and intravenous colistin-based combination therapy showed a trend towards lower infection-related mortality (RR, 0.75; $P = 0.09$; 95% CI, 0.53–1.05; $I^2 =$

0%; Figure 6).

4) Nephrotoxicity

Intravenous colistin-based combination therapy resulted in significantly lower nephrotoxicity as compared with colistin monotherapy (RR, 0.77; $P = 0.03$; 95% CI, 0.60–0.98; $I^2 = 0.0\%$; Figure 7).

Discussion

This meta-analysis included seven RCTs [22–28] involving 433 patients treated with intravenous colistin in combination with other antibiotics and 426 patients treated with intravenous colistin alone. There are some inconsistent outcomes among the 7 studies included, which may be related to variations in individual study characteristics, including patient population with different complications, study place, clinical setting, pathogen and sample sizes. Therefore, the present meta-analysis increases the likelihood of identifying true efficacy and nephrotoxicity of intravenous colistin-based combination strategy against carbapenem-resistant gram-negative infections.

Of the seven studies [22–28] included, six [22–27] reported microbiological response, i.e., microbial eradication. Our meta-analysis found that colistin-based combination therapy showed a trend towards higher microbial eradication than colistin monotherapy, which indicated that colistin-based combination therapy may be better than colistin monotherapy. Further analysis found that of these six studies included, five by Aydemir et al., [22] Durante-Mamgani et al., [23] Makirs et al., [25] Park et al. [28] and Sirijatuphat et al. [24] showed this trend. Our results confirmed the results found in most of these studies. Subgroup analysis found that colistin-based combination regimen, especially colistin plus rifampicin regimen, have significantly higher eradication rates to *A. baumannii*, indicating this combination regimen have a greater advantage in the treatment of carbapenem-resistant *A. baumannii* infections than colistin alone.

Four studies [22–25] included in this meta-analysis were involved in infection-related mortality, pathogen of which was all *A. baumannii*. Intravenous colistin-based combination therapy was found a trend towards lower mortality. This was because these studies [22–25] all showed this trend. This finding was consistent with the result of microbiological response index, further indicating that an intravenous colistin-based combination regimen may be superior to colistin alone in the treatment of carbapenem-resistant *A. baumannii* infection.

Overall analysis and subgroup analysis on combination regimen for colistin plus rifampicin and on carbapenem-resistant *A. baumannii* infections showed that all-cause or crude mortality was not significantly different between the patients receiving colistin-based combination therapy and the patients receiving intravenous colistin monotherapy, which was similar to the result reported by Cheng et al. [21]. Of the seven RCTs [22–28] included, only study by Abdelsalam et al. [27] demonstrated significantly higher all-cause mortality in patients treated with colistin monotherapy than in those treated with colistin-based combination therapy (RR, 2.60; 95%CI, 1.06–6.39), other studies [22–26, 28] showed no difference in all-cause mortality. Therefore, our meta-analysis did not obtain positive results, too. All-cause mortality was not only related to the severity of infection and time of administration, but was also correlated with other pathophysiological factors such as older age, higher Charlson score, congestive heart failure, chronic kidney disease, diabetes mellitus, a need for hemodynamic support, dialysis, higher Sequential Organ Failure Assessment (SOFA) score, and higher creatinine level [31]. Therefore, the index of all-cause mortality can not really reflect the efficacy of antibacterial drugs.

Four studies [23, 24, 26, 27] reported the risk of nephrotoxicity according to risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria. Our meta-analysis found that colistin-based combination therapy was associated with significantly lower nephrotoxicity than colistin monotherapy, which differed from the result reported by Cheng et al. [21]. This was because these four studies all showed this trend. Of these four studies, [23, 24, 26, 27] nephrotoxicity was

mainly correlated with the factor of infection besides colistin autonomous induction. The antibiotic combination regimen differed in these four RCTs, [23, 24, 26, 27] where rifampicin, fosfomycin, and meropenem were administered. Rifampicin, fosfomycin, and meropenem were not found to have protection against nephrotoxicity of colistin up to now. As mentioned above, our meta-analysis demonstrated that the combination therapy showed a trend towards lower infection-related mortality and significantly higher microbiological response. Therefore, we believe that lower nephrotoxicity in patients treated with combination regimens may be related to infection control.

Novelty and limitations

Our meta-analysis has some strengths. Besides an unrestricted search process, duplicate review procedures for the search, sensitivity analysis, and assessments of the risks of biases, only RCTs were included in the meta-analysis. Therefore, the risk of bias in the present meta-analysis should be greatly minimized, and the level of evidence was stronger. However, this meta-analysis also has several limitations. Firstly, although seven RCTs were included, six studies [22–27] were open label; thus, performance bias, the blinding of participants and personnel, may have been present. Secondly, as we know, interstudy heterogeneity and publication bias are major limitations correlated with meta-analyses. Heterogeneity can be caused by many factors such as patient population with different complication, sample sizes, clinical setting and antibacterial regimen. We found that there was obvious heterogeneity in analyzing microbiological response. This was due to larger sample sizes and different pathogen in the study by Paul et al. [26]. When the study by Paul et al. [26] was removed, I^2 value was significantly decreased and P value was above 0.05 (data not shown). As for publication bias, we could not obtain observation due to not enough study numbers. Thirdly, although a wide search in three different databases was used to find studies for inclusion in the meta-analysis, it is impossible to confirm that all available studies comparing the efficacy and nephrotoxicity of intravenous colistin or polymyxin B-based combination therapy and colistin or polymyxin B monotherapy were included, presenting another main limitation of this meta-analysis.

Conclusions

Our meta-analysis found some encouraging results based on higher quality evidence. Combined intravenous therapy based on colistin showed a trend towards higher microbiological response, lower infection-related mortality and significantly lower nephrotoxicity than colistin monotherapy against carbapenem-resistant gram-negative bacterial infections, especially *A. baumannii* infection.

Abbreviations

RCT: randomized controlled trials; PRISMA-P: preferred reporting items for systematic reviews and meta-analysis protocols; MIU: million international units; RR: risk ratio; CI: confidence interval; RIFLE: risk, injury, failure, loss, and end-stage renal disease.

Declarations

Funding

There was no external funding for this research.

Availability of data and materials

All data and materials used in this research are freely available. References have been provided.

Authors' contributions

ZDL designed the study, searched the literature, selected the study, analyzed and interpreted data, and drafted and revised the article. ZKX, XYW, QS and BQX participated in the literature search and study selection. GZW took part in assessments of quality. The authors declare that there are no competing interests regarding the publication of this paper.

Ethics approval and consent to participate

Ethical approval was not applicable for this systematic review and meta-analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of the included studies.

Author/ Publication Year	Study Year	Country	Bacteria	Setting	Infection Type (%)	Usage of IV Colistin Dose	Combination regimen
Aydemir, 2013 ²²	2011- 2012	Turkey	Carbapenem- resistant	ICU	VAP (100)	300 mg colistin based activity/ day, t.id. (9 MIU per day)	Colistin+ Rifampicin
Durante- Mangoni, 2013 ²³	2010- 2011	Italy	A. baumannii Extensive-drug resistant	ICU	VAP (69), BSI (20), HAP (9), cIAI (2)	2 MIU every 8 h	Colistin+ Rifampicin
Sirijatuphat, 2014 ²⁴	2010- 2011	Thailand	Carbapenem- resistant A. baumannii	ICU and ward	Pneumonia (76.6), BSI (5.4), UTI (5.4), IAI (6.4), SSTI (3.2), CNSI (1.0), other (2.1)	5 mg colistin based activity /kg/ day (9 MIU per day)	Colistin+ Fosfomycin
Paul, 2018 ²⁶	2013- 2016	Israel, Greece, Italy	Carbapenem- resistant gram-negative bacteria, including A. baumannii, Enterobacteriaceae, Pseudomonas, and others	ICU and ward	VAP/HAP (44.8), BSI (42.6), UTI (6.4), pVAP (6.2)	9 MIU loading, followed by 4.5 MIU every 12 h	Colistin+ Meropenem
Makirs, 2018 ²⁵	-	Greece	Carbapenem- resistant A. baumannii	ICU	VAP (100)	3 MIU t.i.d.	Colistin+Ampicillin- sulbactam
Park, 2018 ²⁸	2016- 2018	Korea	Colistin-resistant A. baumannii	Ward	VAP (100)	No reported.	Colistin+ Rifampicin
Abdelsalam, 2018 ²⁷	2016- 2016	Egypt	Carbapenem- resistant K. pneumoniae	ICU	HAP (100) with UTI(16.6) IAI(11.7) SSTI (1.7) CRI(15.0) BSI(46.7) SSI(3.3)	9 MIU loading, followed by 3 MIU every 8 h (CLCr>50 mL/min), 4.5 MIU every 24 h (CLCr 20 - 50 mL/min).	Colistin+ Meropenem

ICU, intensive care unit; VAP, ventilator-associated pneumonia; BSI, bloodstream infection; HAP, hospital-acquired pneumonia; cIAI, complicated intra-abdominal infection; UTI, urinary tract infection;

SSTI, skin and soft tissue infection; CNSI, central nervous system infection; MIU, million international units; IV, intravenous; t.i.d, three times per day.

Table 2. Outcomes of combination therapy versus monotherapy

Author and publication year	Microbial response		Crude mortality		Infection-related death		Nephrotoxicity	
	Combination	Monotherapy	Combination	Monotherapy	Combination	Monotherapy	Combination	Monotherapy
Aydemir, 2013 ²²	15/21*	13/22	13/21	16/22	8/21	14/22	NR	NR
Durante-Mangoni, 2013 ²³	63/104	47/105	45/104	45/105	22/104	28/105	24/101	29/101
Sirijatuphat, 2014 ²⁴	47/47	38/47	22/47	27/47	10/47	13/47	25/47	28/47
Paul, 2018 ²⁶	135/208	136/198	94/208	86/198	NR	NR	18/88	27/77
Makirs, 2018 ²⁵	10/20	1/19	7/20	4/19	2/20	2/19	NR	NR
Park, 2018 ²⁸	3/3	2/5	1/3	1/5	NR	NR	NR	NR
Abdelsalam, 2018 ²⁷	NR	NR	5/30	13/30	NR	NR	6/30	8/30

*: number of events / total number. NR, the outcome was not reported.

Figures

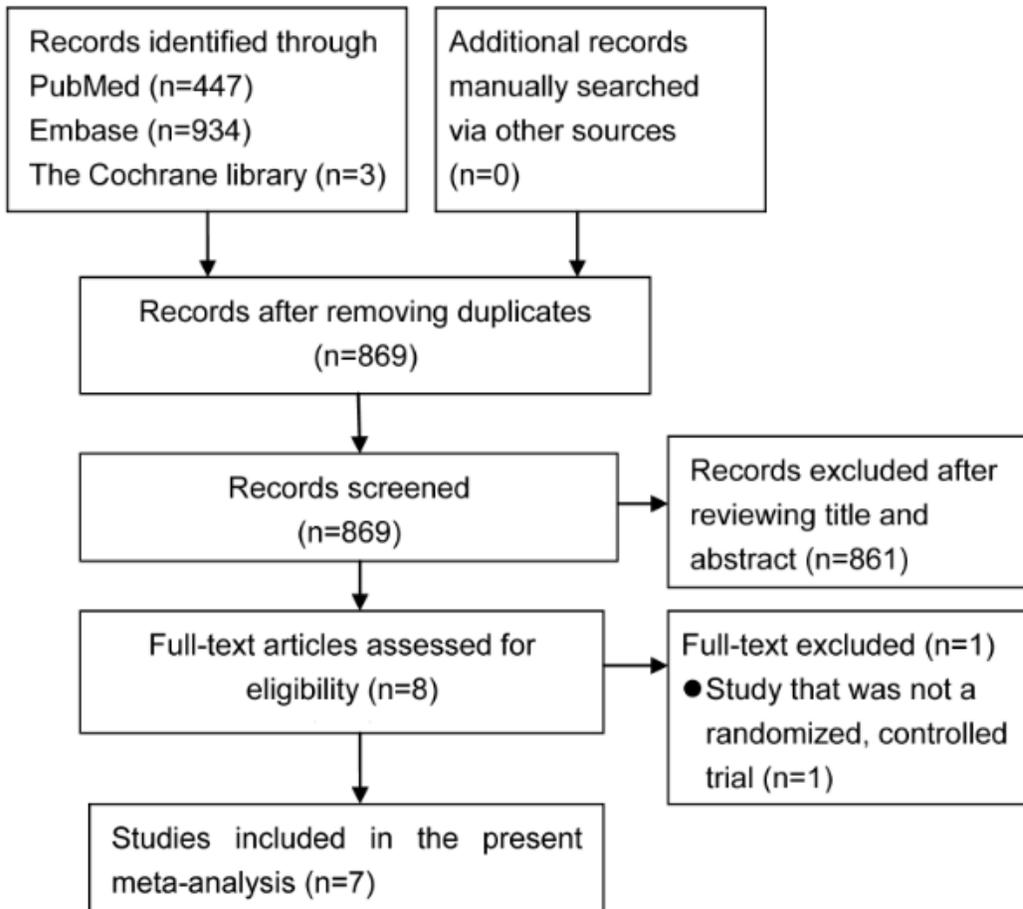


Figure 1

Flow diagram of the study selection process.

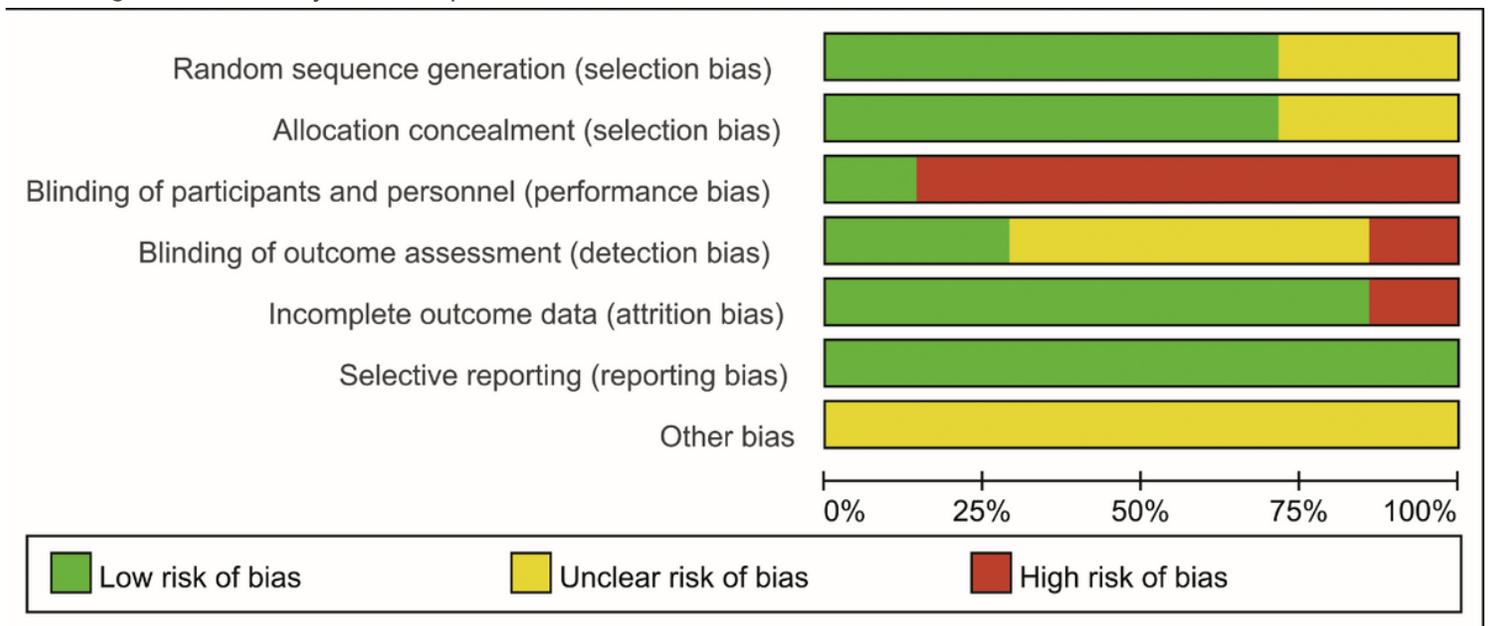


Figure 2

Summary of risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdelsalam 2018	+	+	-	+	+	+	?
Aydemir 2013	+	+	-	?	+	+	?
Durante-Mangoni 2013	+	+	-	?	+	+	?
Makirs 2018	?	?	-	-	-	+	?
Park 2018	+	+	+	?	+	+	?
Paul 2018	+	+	-	+	+	+	?
Sirijatuphat 2014	?	?	-	?	+	+	?

Figure 3

Risk of various biases per study.

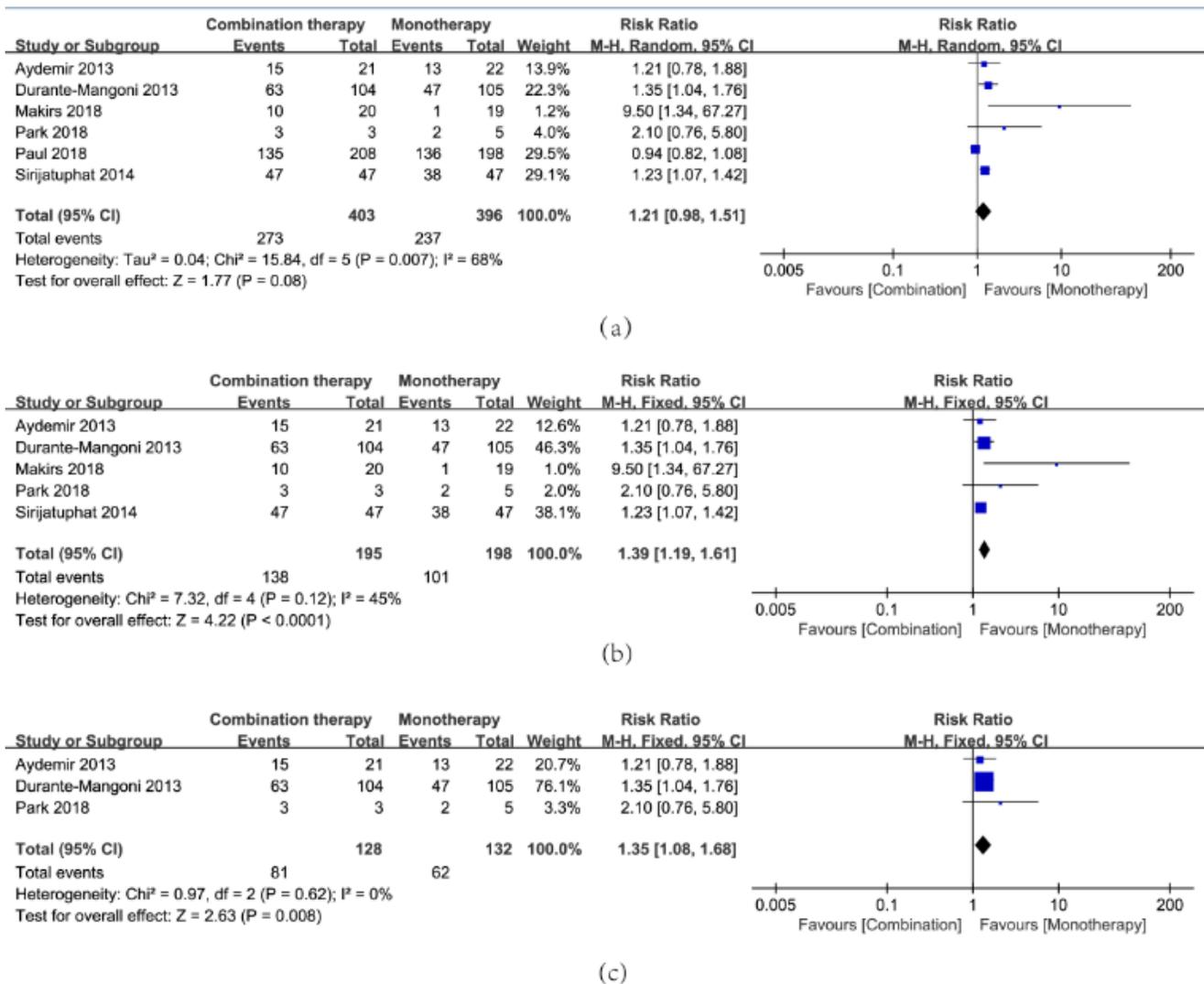
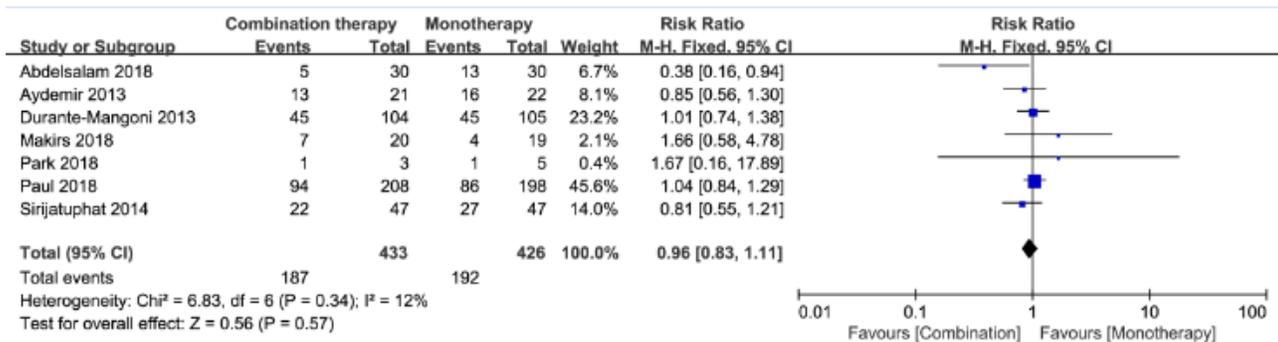
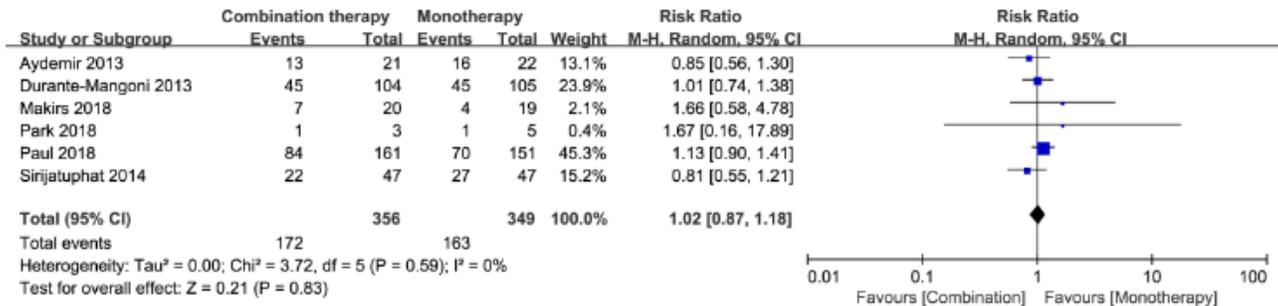


Figure 4

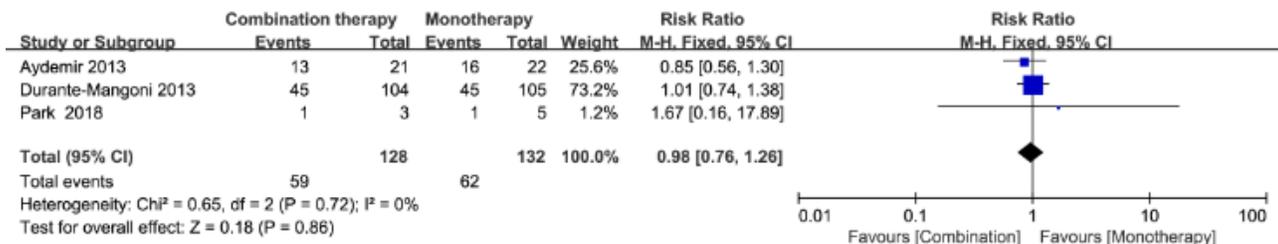
Forest plot depicting the risk ratio (RR) of microbiological response in patients treated with intravenous colistin-based combination regimen versus colistin alone. (a) overall analysis; (b) subgroup analysis on *A. baumannii* infections; (c) subgroup analysis on combination regimen for colistin plus rifampicin.



(a)



(b)



(c)

Figure 5

Forest plot depicting the risk ratio (RR) of all-cause mortality in patients treated with intravenous colistin -based combination regimen versus colistin alone. (a) overall analysis; (b) subgroup analysis on *A. baumannii* infections; (c) subgroup analysis on combination regimen for colistin plus rifampicin.

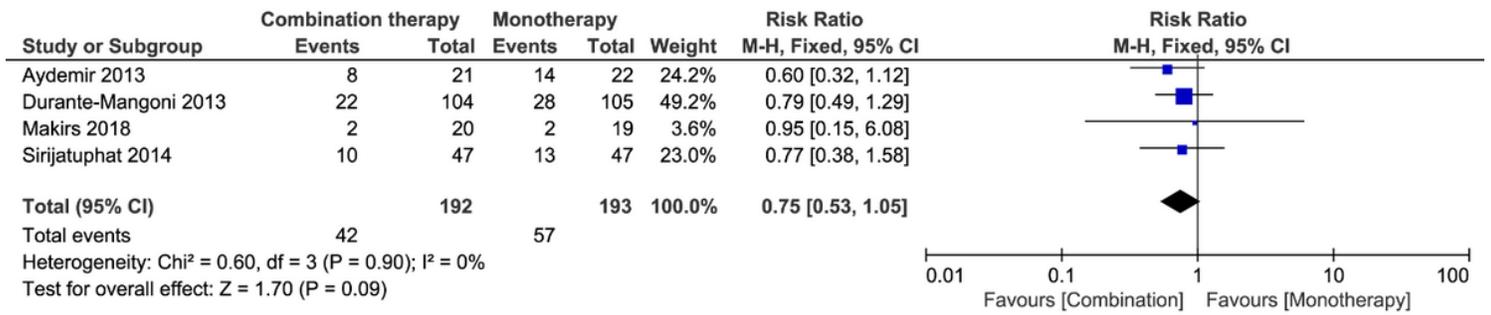


Figure 6

Forest plot depicting the risk ratio (RR) of infection-related mortality in patients treated with intravenous colistin-based combination regimen versus colistin alone.

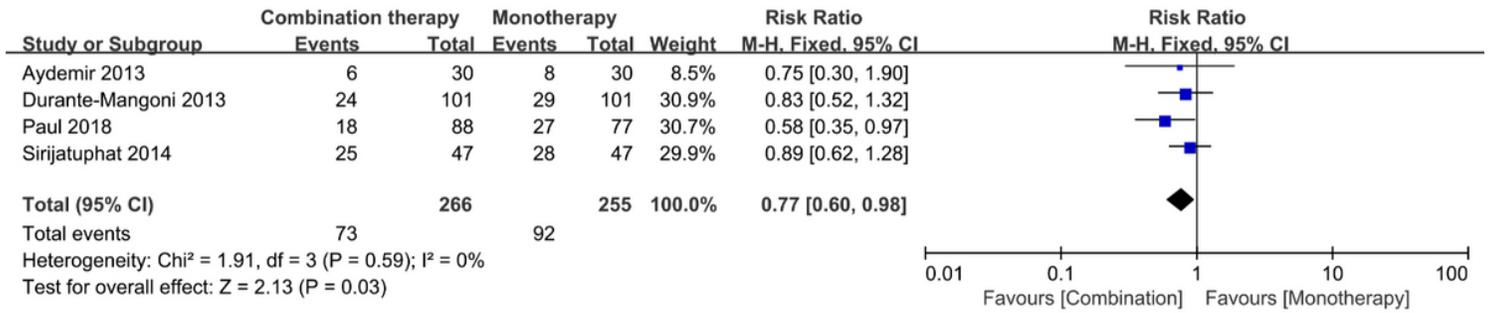


Figure 7

Forest plot depicting the risk ratio (RR) of nephrotoxicity in patients treated with intravenous colistin-based combination regimen versus colistin alone.