International Journal of Antimicrobial Agents 53 (2019) 383–400

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Safety and efficacy of colistin alone or in combination in adults with *Acinetobacter baumannii* infection: A systematic review and meta-analysis

Jin Wang, Hui Niu, Rui Wang, Yun Cai*

Center of Medicine Clinical Research, Department of Pharmacy, PLA General Hospital, 28 Fu Xing Road, Beijing 100853, P.R. China

ARTICLE INFO

Article history:
Received 21 May 2018
Accepted 27 October 2018

Editor: Jean-Marc Rolain

Keywords:
Colistin
Acinetobacter baumannii
Monotherapy
Combination therapy
Meta-analysis

ABSTRACT

This review comprehensively assessed the safety and efficacy of colistin alone or in combination in adults with *Acinetobacter baumannii* infection. PubMed, Embase and the Cochrane Library were searched from inception to March 2018 for studies evaluating colistin monotherapy compared with other antibiotic therapy or colistin-based combination therapy for the treatment of *A. baumannii* infection in adults. Efficacy outcomes were clinical response and microbiological cure. Safety outcomes were mortality and nephrotoxic adverse events. A total of 4 randomised controlled trials (RCTs) and 14 observational studies were identified, including 7 reporting colistin versus other antibiotics and 12 reporting colistin monotherapy versus colistin-based combination therapy. Overall clinical response, microbiological response and mortality did not differ significantly between colistin monotherapy versus other antibiotics. However, the incidence of nephrotoxicity was significantly higher in colistin monotherapy (OR = 2.50, 95% CI 1.05–5.98; $P = 0.04$). No significant differences were detected in clinical response and >28-day mortality between colistin monotherapy and combination therapy. However, colistin-based combination therapy showed an increased microbiological response (OR = 0.49, 95% CI 0.32–0.74; $P = 0.0009$) and decreased incidence of nephrotoxicity (OR = 1.66, 95% CI 0.99–2.78; $P = 0.05$). In conclusion, colistin alone is as effective as other antibiotics for the treatment of *A. baumannii* infection but has a higher risk of nephrotoxicity. Colistin-based combination therapy demonstrated a microbiological benefit and no higher risk of nephrotoxicity compared with monotherapy. High-quality RCTs are still needed to confirm the beneficial role of colistin-based combination therapy.

1. Introduction

Acinetobacter baumannii is an important opportunistic, nosocomial, Gram-negative bacterium that was listed as one of the six most important multidrug-resistant (MDR) pathogens in hospitals worldwide by the Infectious Diseases Society of America in 2006 [1,2]. It is also classified at the highest level of 'critical' by the World Health Organization (WHO) because it is resistant to a large number of antimicrobial agents, including carbapenems [3]. *Acinetobacter baumannii* causes a broad range of severe infections, including ventilator-associated pneumonia (VAP), bloodstream infection, skin and soft-tissue infection, urinary tract infection, wound infection and secondary meningitis [4]. VAP and bloodstream infections are the most important, with the highest mortality rates at ca. 35% [1].

Acinetobacter baumannii has the ability to acquire resistance to multiple classes of antimicrobial agents, resulting in extremely difficult to treat infections caused by MDR strains [5,6]. Even for carbapenems, which have been considered appropriate agents to treat MDR *A. baumannii* (MDR-AB) infections, a worldwide surge of carbapenem resistance has recently been reported [7]. Clinically effective therapeutic options have almost been reduced to tigecycline and colistin [8,9]. Although tigecycline has been used for only ca. 10 years, a significant percentage of resistance (15%) was observed in a study of the pooled prevalence of antibiotic resistance [10]. Colistin is especially important when tigecycline is found to be non-susceptible. The pooled antibiotic resistance study also showed that colistin resistance remained lower at 1.3–1.4% during 2006–2016, indicating that colistin is still the most active agent against *A. baumannii* infections [10]. However, resistance to colistin is also emerging. A recent study from Europe reported that 45.5% of 65 clinical *A. baumannii* isolates recovered from respiratory tract samples from patients with VAP were resistant to colistin [11].

* Corresponding author. Tel.: +86 10 6693 7166; fax: +86 10 8821 4425.
E-mail address: caicai_hh@126.com (Y. Cai).

https://doi.org/10.1016/j.ijantimicag.2018.10.020
0924-8579/

Chen et al. [12] published a meta-analysis of colistin for the treatment of *A. baumannii* infection in adults and neonates (only one study [13]), which included studies published before March 2014. Considering the great difference between adults and neonates, mixing them in the same meta-analysis may result in greater heterogeneity. Meanwhile, several clinical studies on colistin monotherapy or combination therapy have been published recently. Thus, in this study a systematic review and meta-analysis was conducted to comprehensively update the efficacy and safety of colistin alone or in combination for the treatment *A. baumannii* infections with a focus on adult patients.

2. Methods

2.1. Protocol and guidelines

The protocol of this study can be found at PROSPERO with the registration no. CRD42018093531 [14]. The systematic review was conducted and presented in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

2.2. Data sources and search strategy

Two authors (JW and HN) systematically searched the bibliographic databases, including PubMed, Embase and the Cochrane library, starting from their inception to March 2018, with no restriction on language, publication date, study design or study quality. Search terms were combined as follows: ('colistin' OR 'polymyxin E') AND ('*Acinetobacter baumannii*'). Articles with the relevant terms from each database were identified and were imported into Endnote Library to delete duplicate records. Previously published systematic reviews were reviewed to identify any additional studies that may have been missed in the primary literature search.

2.3. Inclusion and exclusion criteria

All controlled studies, including randomised controlled trials (RCT) and retrospective or prospective cohort studies, were included if they investigated the efficacy or safety of colistin for the treatment of *A. baumannii* infection in adult patients. Studies were included if they reported one or more of the following outcomes: efficacy-related outcomes including clinical response and/or microbiological response; safety-related outcomes including mortality and/or nephrotoxicity; and the most common adverse effects of colistin. Colistin could have been administered alone compared with another antibiotic regimen or compared with colistin-based combination therapy. In vitro, animal and pharmacokinetic studies as well as protocol papers were all excluded. Articles with a study population aged <18 years were excluded. Studies including polymyxin B as the treatment regimen were excluded. Articles were also excluded if there were also pathogens other than *A. baumannii*.

2.4. Review process and data extraction

To determine the eligibility of identified trial reports, two authors (JW and HN) independently screened the titles and abstracts. Full texts were obtained where necessary. Differences of opinion were resolved by discussion between the authors and adjudicated by the lead author (YC) if necessary. Data were manually extracted from the eligible full-text articles. Author, year of publication, region, study type, resistance pattern of *A. baumannii*, and total number and mean age of subjects included in the experimental and control groups were extracted.

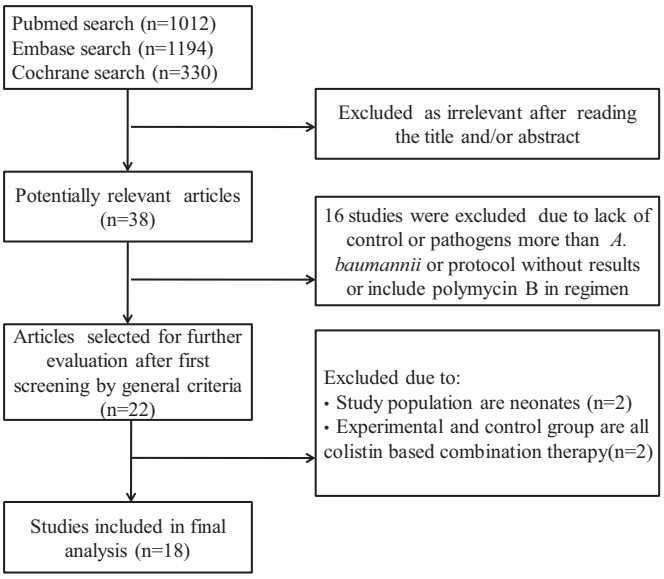


Fig. 1. Flow diagram of the study selection process.

2.5. Statistical analysis

Data were entered into the Cochrane Review Manager software RevMan v.5.3 (The Cochrane Collaboration, Oxford, UK). Differences were expressed as the odds ratio (OR) with 95% confidence intervals (CI) for dichotomous outcomes. The significance of the pooled ratios was determined by *Z*-test, and a *P*-value of <0.05 was considered statistically significant. Heterogeneity of trial results was assessed by calculating a χ^2 test of heterogeneity and the I^2 measure of inconsistency. A DerSimonian and Laird random-effects model was used for all outcomes throughout the meta-analysis. Publication bias was assessed by examining the funnel plot.

3. Results

3.1. Characteristics of included trials

As shown in Fig. 1, the initial search resulted in 1012, 1194 and 330 articles from PubMed, Embase and Cochrane Library, respectively. After excluding duplicates and irrelevant studies by reading the title and/or abstract, 38 potentially relevant articles remained. Sixteen articles were excluded because of a lack of control, pathogens other than *A. baumannii*, treatment including polymyxin B or protocol without required outcomes. Two articles were excluded because the study population included neonates [13,16]. Another two articles were excluded because the experimental and control groups were both colistin-based combination therapy [17,18]. Finally, 18 studies were included in the meta-analysis [19–36].

The main characteristics of the 18 included studies are shown in Table 1. Seventeen of the studies were from Asia and Europe, including Korea [19–21], Thailand [22], Taiwan [23], Israel [24,25], Turkey [26–30], Spain [31,32], Greece [25,33,34] and Italy [25,35]. Only one study was from South Africa [36]. For colistin regimen versus other antibiotic regimen group, seven studies involving 644 patients were included. Two of them were prospective cohort studies and the other five studies were retrospective cohort studies. For colistin monotherapy versus colistin-based combination therapy, 12 studies (4 RCTs, 6 retrospective cohort studies and 2 prospective cohort study) with 1386 patients were included. A retrospective study by Chuang et al. including 294 MDR-AB pneumonia patients from Taiwan [23] was included in the colistin versus other

Table 1
Characteristics of studies included in the meta-analysis.

Reference	Region	Study type	Bacteria	Type of infection	Treatment group			Control group			Definition of microbiological eradication or cure
					Antibiotic[a]	Age (years)[b]	No. of patients	Antibiotic[c]	Age (years)[b]	No. of patients	
Colistin versus other antibiotics											
Garnacho-Montero et al., 2003 [31]	Spain	Prospective cohort study	MDR-AB: susceptible exclusively to colistin in colistin group; besides colistin, also susceptible to IPM/CIS in IPM/CIS group	VAP	Colistin: 2.5–5.0 mg/kg/day in 3 divided doses	56.9 ± 13.1	21	IPM/CIS: 2–3 g/day	64.5 ± 11	14	Tracheal aspirates examined to confirm eradication of the micro-organism. Microbiological eradication considered to have occurred if the aspirate culture was negative for AB
Betrosian et al., 2008 [33]	Greece	Prospective cohort study	MDR-AB: resistant to all antibiotics routinely tested, including penicillins, aminoglycosides, SAM, cephalosporins, aztreonam, carbapenems, fluoroquinolones and tetracyclines, excluding colistin	VAP	Colistin: 3 MU q8h	67 ± 9	15	SAM 9 g q8h	72 ± 5	13	Bacteriological success defined by eradication of AB isolates as noted on follow-up BAL
Gounden et al., 2009 [36]	South Africa	Retrospective cohort study	MDR-AB: isolates in the colistin group were resistant to all antimicrobials tested except colistin. All isolates in the tobramycin group were susceptible to tobramycin	ICU-acquired AB infection	Colistin: 2 MU q8h	43.5 ± 15.6	32	Tobramycin: 5–6 mg/kg/day	45.6 ± 18.2	32	Microbiological clearance defined as ≥2 consecutive negative cultures for AB from all sites sampled within 10 days of initiation of the antimicrobial, with no subsequent positive cultures
Chuang et al., 2014 [23]	Taiwan	Retrospective cohort study	MDR-AB: non-susceptible to ≥1 agent in ≥3 antimicrobial categories	Pneumonia	Colistin: 2.5–5 mg/kg/day CBA in 2–3 divided doses	63.7 ± 19.5	119	Tigecycline: 100 mg loading dose, followed by 50 mg q12h	63.8 ± 17.9	175	–
Kwon et al., 2014 [19]	Korea	Retrospective cohort study	XDR-AB: susceptible only to colistin or minocycline	Pneumonia, bacteraemia, etc.	Colistin: 75–300 mg/day	59.0 ± 19.2	39	Tigecycline: 50–100 mg/day	60.1 ± 12.3	16	Negative conversion defined by 2 consecutive negative culture results after use of colistin or tigecycline

(*continued on next page*)

Table 1 (*continued*)

Reference	Region	Study type	Bacteria	Type of infection	Treatment group			Control group			Definition of microbiological eradication or cure
					Antibiotic[a]	Age (years)[b]	No. of patients	Antibiotic[c]	Age (years)[b]	No. of patients	
Kim et al., 2016 [20]	Korea	Retrospective cohort study	MDR-AB: non-susceptible to ≥1 agent in ≥3 antimicrobial categories. XDR-AB: non-susceptible to ≥1 agent in all but two or fewer antimicrobial categories	HAP or VAP	Colistin-based: 5 mg/kg CBA loading dose, followed by 150 mg q12h	67 (IQR 57–75)	40	Tigecycline-based: 100 mg loading, followed by 50 mg q12h	72 (IQR 64–76)	30	Microbiological success defined as eradication of the pathogen (e.g. no growth of the pathogen in final culture of specimens during entire hospitalisation)
Zalts et al., 2016 [24]	Israel	Retrospective cohort study	CRAB: resistant to carbapenems and susceptible to SAM and/or colistin	VAP	Colistin: 2 MU of CBA in 3 divided doses	56.7 ± 20.4	66	SAM: 3 g q6h	50.3 ± 19.0	32	Microbiological failure defined as continued AB growth in respiratory sample culture 1 week after initiation of appropriate antibacterial therapy
Colistin monotherapy versus colistin-based combination therapy											
Hang et al., 2009 [21]	Korea	Retrospective cohort study	MDR-AB: resistant to all or ≥2 of the antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones and aminoglycosides	VAP	Colistin: 2.5 mg/kg q12h	62.5 ± 17.5	22	Colistin + CSL or SAM Colistin + minocycline Colistin + CSL + minocycline Colistin + CSL + SXT	57.0 ± 16.5	19	–
Simsek et al., 2012 [26]	Turkey	Retrospective cohort study	MDR-AB: susceptible to polymyxins but resistant to agents from antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones and aminoglycosides	VAP, BSI etc.	Colistin: 2.5–5 mg/kg/day CBA	51.71 ± 18.82	20	Colistin + rifampicin Colistin + carbapenem Colistin + tigecycline + rifampicin Colistin + tigecycline Colistin + carbapenem + rifampicin Colistin + SAM	51.71 ± 18.82	31	Negative urine culture for UTI, negative CSF culture three times subsequent to initiation of colistin for nosocomial meningitis and negative culture of sample related to infection
Durante-Mangoni et al., 2013 [35]	Italy	RCT	XDR-AB: resistant to carbapenems (MIC ≥16 mg/L) and all other antimicrobial drug classes, except colistin	HAP, VAP, BSI, cIAI	Colistin: 2 MU q8h	61 ± 15.7	105	Colistin + rifampicin: 600 mg q12h	62 ± 15.1	104	Microbiological eradication defined as disappearance of AB in all follow-up cultures from the primary source of infection (i.e. blood, BAL or bronchial aspirate, drainage fluids) during treatment

(*continued on next page*)

Table 1 (*continued*)

Reference	Region	Study type	Bacteria	Type of infection	Treatment group			Control group			Definition of microbiological eradication or cure
					Antibiotic[a]	Age (years)[b]	No. of patients	Antibiotic[c]	Age (years)[b]	No. of patients	
Aydemir et al., 2013 [27]	Turkey	RCT	CRAB	VAP	Colistin: 300 mg/day CBA in 3 divided doses	63 ± 17	22	Colistin + rifampicin: 600 mg/day	58 ± 23	21	Cultures of bronchial secretions and blood taken at time of diagnosis and on days 3, 5, 7 and 10 after diagnosis during the follow-up period and at the end of the course of therapy. Microbiological response considered to be achieved if subsequent cultures were negative for AB
Chuang et al., 2014 [23]	Taiwan	Retrospective cohort study	MDR-AB: non-susceptible to ≥1 agent in ≥3 antimicrobial categories	Pneumonia	Colistin: 2.5–5 mg CBA/kg/day in 2–3 divided doses	63.7 ± 19.5	104	Colistin + carbapenem	63.8 ± 17.9	15	–
Batirel et al., 2014 [28]	Turkey	Retrospective cohort study	XDR-AB: non-susceptible to ≥1 agent in all but two or more antimicrobial categories	BSI	Colistin: 5 mg/kg/day CBA in 2–3 divided doses	58.3 ± 20.5	36	Colistin + carbapenem Colistin + sulbactam Colistin + others: imipenem 500 mg q6h, meropenem 1 g q8h, doripenem 500 mg q8h, sulbactam 1.5 g q6h, tigecycline 50 mg q12h after 100 mg loading dose, amikacin 1 g qd, netilmicin 2 mg/kg q8h, gentamicin 160 mg q12h, rifampicin 600 mg qd, TZP 4.5 g q8h	59.1 ± 19.6	214	Microbiological eradication of AB in any control blood cultures
Lopez-Cortes et al., 2014 [32]	Spain	Prospective cohort study	MDR-AB	Sepsis	Colistin: 2 MU q8h	60 (IQR 49–74)	46	Colistin + tigecycline Colistin + carbapenem Colistin + sulbactam Colistin + aminoglycoside Colistin + rifampicin Colistin + tigecycline + carbapenem + aminoglycoside Colistin + tigecycline + aminoglycoside	61 (IQR 64–77)	23	–
Kalin et al., 2014 [29]	Turkey	Retrospective cohort study	MDR-AB: resistant to >3 classes of antibiotics (aminoglycosides, antipseudomonal penicillins, carbapenems, cephalosporins, β-lactam/β-lactamase inhibitor, quinolones; in addition, colistin and tigecycline were tested occasionally)	VAP	Colistin: 2.5 mg/kg q12h	52 (19–96)	52	Colistin + sulbactam: 3 g q8h	63 (20–89)	37	Bacteriological clearance defined as eradication of MDR-AB, and bacteriological failure defined as persistence of MDR-AB on follow up culture

(*continued on next page*)

Table 1 (*continued*)

Reference	Region	Study type	Bacteria	Type of infection	Treatment group			Control group			Definition of microbiological eradication or cure
					Antibiotic[a]	Age (years)[b]	No. of patients	Antibiotic[c]	Age (years)[b]	No. of patients	
Sirijatuphat et al., 2014 [22]	Thailand	RCT	CRAB	Pneumonia, bacteraemia, UTI, etc.	Colistin: 5 mg/kg/day CBA	69.2 ± 16.3	47	Colistin + fosfomycin: 4 g q12h	67.4 ± 17.2	47	Microbiological culture of specimens taken from infection site was made on Day 3 after starting study treatment and at the end of treatment with colistin and fosfomycin. Microbiological responses classified as eradication (no target organisms found), persistence, or undetermined
Yilmaz et al., 2015 [30]	Turkey	Retrospective cohort study	MDR-AB: non-susceptible to ≥1 agent in ≥3 antimicrobial categories. XDR-AB: resistant to carbapenems and all other antimicrobial drug classes, except colistin	VAP	Colistin: 75 mg q8h or 150 mg q12h	59.8 ± 21.5	17	Colistin + imipenem 500 mg q6h Colistin + meropenem 1 g q8h Colistin + sulbactam 1 g q8h	59.6 ± 20.5	53	Microbiological response defined as no bacterial growth from site-specific cultures at end of colistin therapy
Paul et al., 2018 [25]	Israel, Greece, Italy	RCT	CRAB	Bacteraemia, HAP, UTI	Colistin: 9 MU loading dose, followed by 4.5 MU maintenance dose q12h	66 ± 16	151	Colistin + meropenem: 2 g q8h	66 ± 18	161	Microbiological failure defined as repeat isolation of bacteria phenotypically identical to the index isolate on or after Day 7 after randomisation
Makris et al., 2018 [34]	Greece	Prospective cohort study	CRAB: resistant to carbapenems but susceptible to colistin	VAP	Colistin: 3 MU q8h	56.6 ± 14.3	19	Colistin + SAM: 6 g q6h	56.9 ± 18.7	20	Tracheal secretions evaluated before extubation or at the end of antimicrobial therapy if the patient was still intubated, to assess AB eradication (microbiological cure)

[a] Doses of colistin in patients with normal renal function are listed. The colistin dose was adjusted for patients with renal impairment.

[b] Age is given as mean ± standard deviation or median (IQR).

[c] Doses of antibiotics other than colistin are listed. The dose of colistin in the combination group is the same as that for the monotherapy group.MDR-AB, multidrug-resistant *Acinetobacter baumannii*; IPM/CIS, imipenem/cilastatin; VAP, ventilator-associated pneumonia; AB, *A. baumannii*; SAM, ampicillin/sulbactam; q8h, every 8 h; BAL, bronchoalveolar lavage; ICU, intensive care unit; CBA, colistin base activity; q12h, every 12 h; XDR-AB, extensively drug-resistant *A. baumannii*; HAP, hospital-acquired pneumonia; IQR, interquartile range; CRAB, carbapenem-resistant *A. baumannii*; q6h, every 6 h; CSL, cefoperazone/sulbactam; SXT, trimethoprim/sulfamethoxazole; BSI, bloodstream infection; UTI, urinary tract infection; CSF, cerebrospinal fluid; RCT, randomised controlled trial; MIC, minimum inhibitory concentration; cIAI, complicated intra-abdominal infection; qd, once daily; TZP, piperacillin/tazobactam.

antibiotic group because it contained the mortality outcome between colistin-based ($n = 119$, including 18 combined with other antibiotics) and tigecycline-based therapy ($n = 175$, including 30 combined with other antibiotics). This study was also included in the colistin monotherapy versus colistin-based combination group because it provided results of the mortality difference between colistin without carbapenem combination ($n = 104$) and colistin plus carbapenem combination ($n = 15$).

3.2. Colistin versus other antibiotic regimens

3.2.1. Efficacy outcomes

Five studies involving 286 patients (181 patients treated with colistin and 105 patients treated with other antibiotics) reported clinical cure and/or improvement. There was no significant difference in clinical response between patients treated with colistin and other antibiotics (OR = 0.91, 95% CI 0.55–1.49; $P = 0.70$; $I^2 = 0\%$) (Fig. 2). Subgroup analysis was also conducted according to different antibiotics in the control group. No significant difference was found in clinical response between colistin and ampicillin/sulbactam (SAM), tigecycline or other antibiotics (Fig. 2).

Six studies involving 280 patients (168 patients treated with colistin and 112 patients treated with other antibiotics) reported negative microbiological response or eradication. The overall microbiological response did not differ significantly between the two groups (OR = 1.13, 95% CI 0.50–2.54; $P = 0.77$; $I^2 = 50\%$). Statistically significant heterogeneity was found not only in all studies ($P = 0.08$, $I^2 = 50\%$) but also in subgroups of SAM ($P = 0.11$; $I^2 = 60\%$) and tigecycline ($P = 0.14$; $I^2 = 54\%$) (Fig. 3).

3.2.2. Safety outcomes

Nephrotoxicity was the main adverse effect of colistin treatment. Data regarding nephrotoxicity were reported in six studies including 526 patients (255 patients treated with colistin and 271 patients treated with other antibiotics). The results showed that nephrotoxicity was significantly more common in patients treated with colistin compared with other antibiotics (OR = 2.50, 95% CI 1.05–5.98; $P = 0.04$; $I^2 = 41\%$). Statistically significant heterogeneity was only found in the subgroups that contained imipenem/cilastatin or tobramycin as control ($P = 0.13$; $I^2 = 41\%$) (Fig. 4).

Hospital mortality or >28-day mortality was provided in seven studies including 644 patients (332 patients treated with colistin and 312 patients treated with other antibiotics). There was no significant difference in mortality between patients treated with colistin compared with other antibiotics (OR = 1.10, 95% CI 0.60–2.02; $P = 0.76$; $I^2 = 58\%$). There was statistically significant heterogeneity in all studies ($P = 0.03$; $I^2 = 58\%$). However, when subgroups were taken into account, no significant heterogeneity was found in three subgroups, whilst mortality in the colistin group was significantly lower than that in the tigecycline group (OR = 0.58, 95% CI 0.39–0.87; $P = 0.008$; $I^2 = 0\%$) (Fig. 5).

3.3. Colistin monotherapy versus colistin-based combination therapy

3.3.1. Efficacy outcomes

Nine studies involving 970 patients compared the clinical response between colistin monotherapy (373 patients) and colistin-based combination therapy (597 patients) for the treatment of MDR-AB infections. There was no obvious difference between colistin monotherapy and combination therapy (OR = 0.76, 95% CI 0.49–1.16; $P = 0.20$; $I^2 = 39\%$) (Fig. 6). Subgroup analysis was also conducted according to different combination antibiotics in the control group. No significant difference was found in any subgroups except for the colistin + SAM combination subgroup. This subgroup included only one study which indicated that clinical success was significantly higher in the colistin + SAM combination group compared with the colistin monotherapy group (OR = 0.08, 95% CI 0.02–0.38; $P = 0.002$) (Fig. 6).

However, compared with colistin combination therapy, colistin monotherapy had a significantly lower microbiological eradication (OR = 0.49, 95% CI 0.32–0.74; $P = 0.0009$; $I^2 = 26\%$) (Fig. 7) from nine studies including 867 patients (327 patients treated with colistin monotherapy and 540 patients treated with combination therapy). Subgroup analysis showed that the colistin combination with rifampicin (OR = 0.54, 95% CI 0.32–0.89; $P = 0.02$; $I^2 = 0\%$), carbapenem or/and sulbactam (OR = 0.41, 95% CI 0.24–0.70; $P = 0.001$; $I^2 = 0\%$) and SAM (OR = 0.06, 95% CI 0.01–0.50; $P = 0.01$) resulted in a significantly higher microbiological eradication than colistin monotherapy (Fig. 7).

3.3.2. Safety outcomes

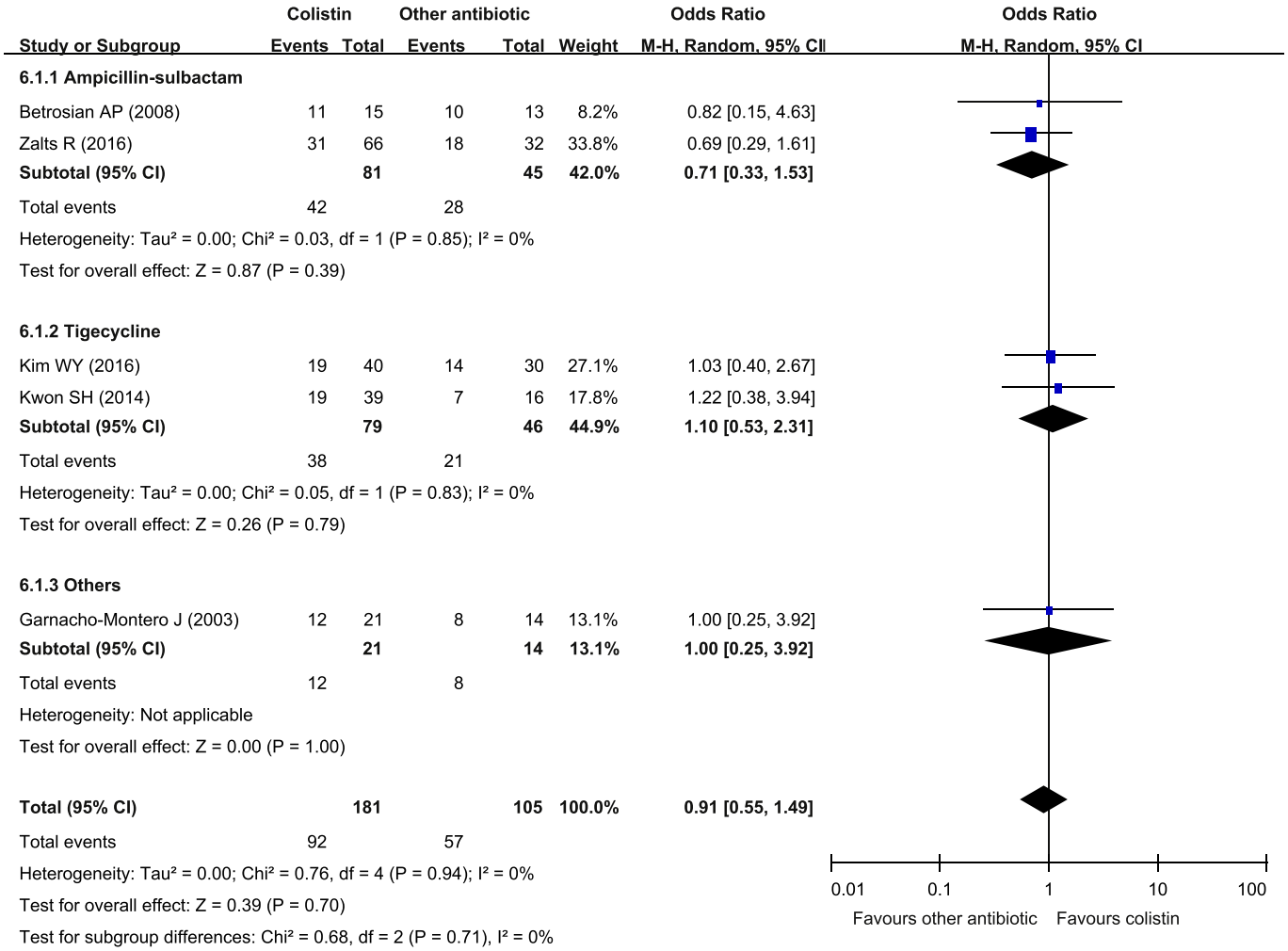
Only four studies including 443 patients (114 patients treated with monotherapy and 329 patients treated with combination therapy) reported nephrotoxicity results, which showed that nephrotoxicity was more common in patients treated with colistin monotherapy compared with colistin-based combination therapy (OR = 1.66, 95% CI 0.99–2.78; $P = 0.05$; $I^2 = 0\%$) (Fig. 8).

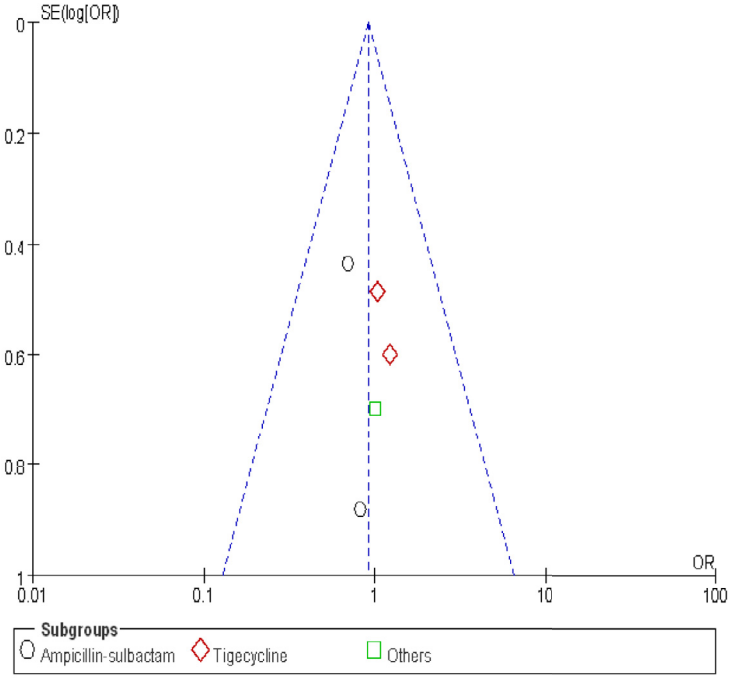
Twelve studies (1367 patients) reported hospital mortality or >28-day mortality and no significant difference was found between colistin monotherapy (628 patients) and colistin-based combination (739 patients) (OR = 1.11, 95% CI 0.82–1.50; $P = 0.49$; $I^2 = 25\%$) (Fig. 9). No significant difference was observed in any subgroups. Four of these studies (373 patients) also reported intensive care unit (ICU)-, VAP- or infection-related mortality. Colistin monotherapy (188 patients) showed a trend of higher mortality compared with combination therapy (187 patients), although the difference was not significant (OR = 1.58, 95% CI 0.99–2.52; $P = 0.06$; $I^2 = 0\%$) (Fig. 10).

4. Discussion

The current meta-analysis of seven controlled studies (two prospective and five retrospective cohort studies) provides evidence that colistin is as effective as other antibiotics, including imipenem/cilastatin, SAM, tobramycin and tigecycline for the treatment of infections caused by MDR-AB. In terms of clinical success and microbiological eradication, colistin showed a similar efficacy to other antibiotics. Although there was no significant difference in mortality overall, colistin treatment showed lower mortality compared with tigecycline treatment. Colistin treatment also significantly increased the risk of nephrotoxicity.

A previous meta-analysis by Chen et al. evaluated the efficacy and safety of colistin for the treatment of MDR-AB infections compared with other antibiotics [12]. It included six controlled studies for analysis, five of which were also described in the current study [19,23,31,33,36]. The current analysis included two more studies published in 2016 with adults as the study population [20,24]. Meanwhile, one study was excluded because it involved neonates [13]. The clinical response and mortality results were consistent between the previous and current meta-analyses. They suggested that colistin may be as safe and efficacious as other antibiotics with a higher microbiological response in the colistin group. However, our updated data did not support colistin as superior to other antibiotics in microbiological response. Moreover, the updated data revealed a significant increase in nephrotoxicity in the colistin group, whereas no difference was found in the previous meta-analysis. Nephrotoxicity is the main adverse drug reaction of colistin. Although less frequent nephrotoxicity colistin has been reported with the improved formulation from colistin sulphate to colistimethate [37], a more recent prospective study showed that nephrotoxicity still developed in 39.3% patients in

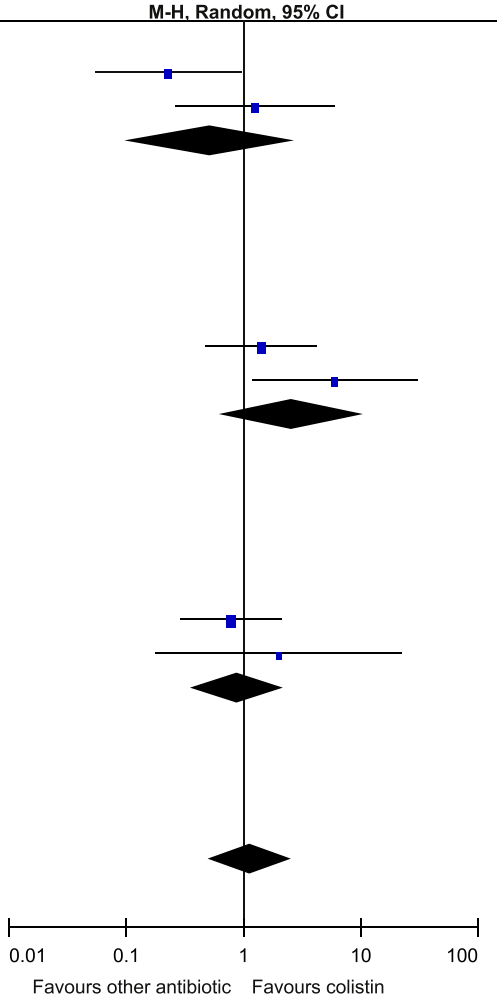


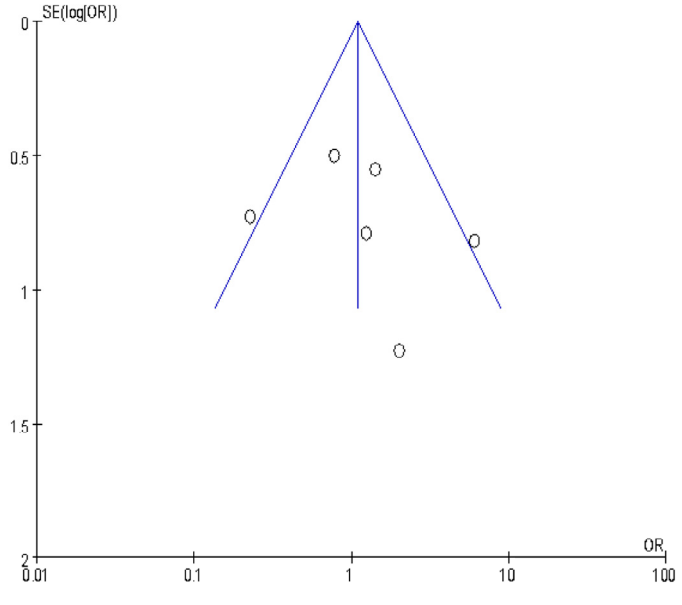


Egger's test results: $t = 2.95$, $p = 0.06$

Fig. 2. Forest plot for clinical success between colistin and other antibiotics. CI, confidence interval.

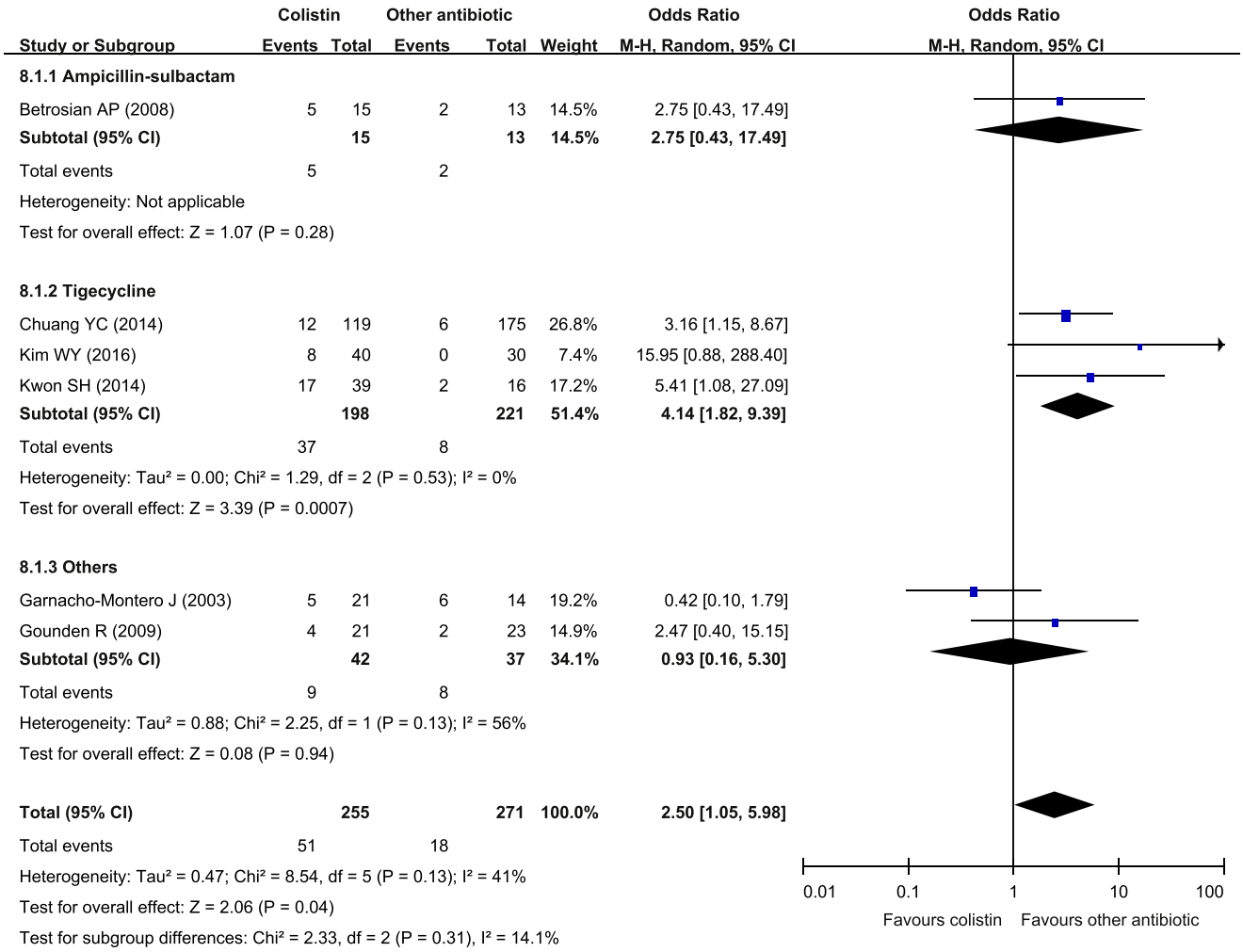
Study or Subgroup	Colistin Events	Total	Other antibiotic Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
7.1.1 Ampicillin-sulbactam						
Zalts R (2016)	17	33	14	17	16.8%	0.23 [0.05, 0.94]
Betrosian AP (2008)	10	15	8	13	15.3%	1.25 [0.27, 5.89]
Subtotal (95% CI)		**48**		**30**	**32.1%**	**0.52 [0.10, 2.75]**
Total events	27		22			
Heterogeneity: Tau² = 0.88; Chi² = 2.53, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 0.77 (P = 0.44)						
7.1.2 Tigecycline						
Kim WY (2016)	12	40	7	30	21.5%	1.41 [0.48, 4.16]
Kwon SH (2014)	18	39	2	16	14.7%	6.00 [1.20, 30.01]
Subtotal (95% CI)		**79**		**46**	**36.2%**	**2.56 [0.63, 10.48]**
Total events	30		9			
Heterogeneity: Tau² = 0.57; Chi² = 2.17, df = 1 (P = 0.14); I² = 54%						
Test for overall effect: Z = 1.31 (P = 0.19)						
7.1.3 Others						
Gounden R (2009)	16	32	18	32	23.1%	0.78 [0.29, 2.08]
Garnacho-Montero J (2003)	6	9	2	4	8.6%	2.00 [0.18, 22.06]
Subtotal (95% CI)		**41**		**36**	**31.7%**	**0.89 [0.36, 2.21]**
Total events	22		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
Total (95% CI)		**168**		**112**	**100.0%**	**1.13 [0.50, 2.54]**
Total events	79		51			
Heterogeneity: Tau² = 0.48; Chi² = 9.92, df = 5 (P = 0.08); I² = 50%						
Test for overall effect: Z = 0.30 (P = 0.77)						
Test for subgroup differences: Chi² = 2.35, df = 2 (P = 0.31), I² = 15.1%						

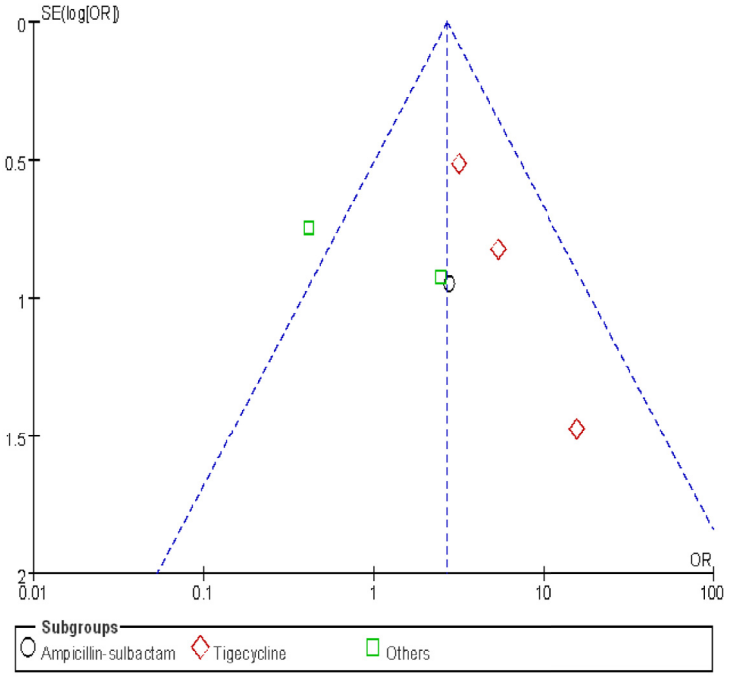




Egger's test results: $t = 4.17$, $p = 0.014$

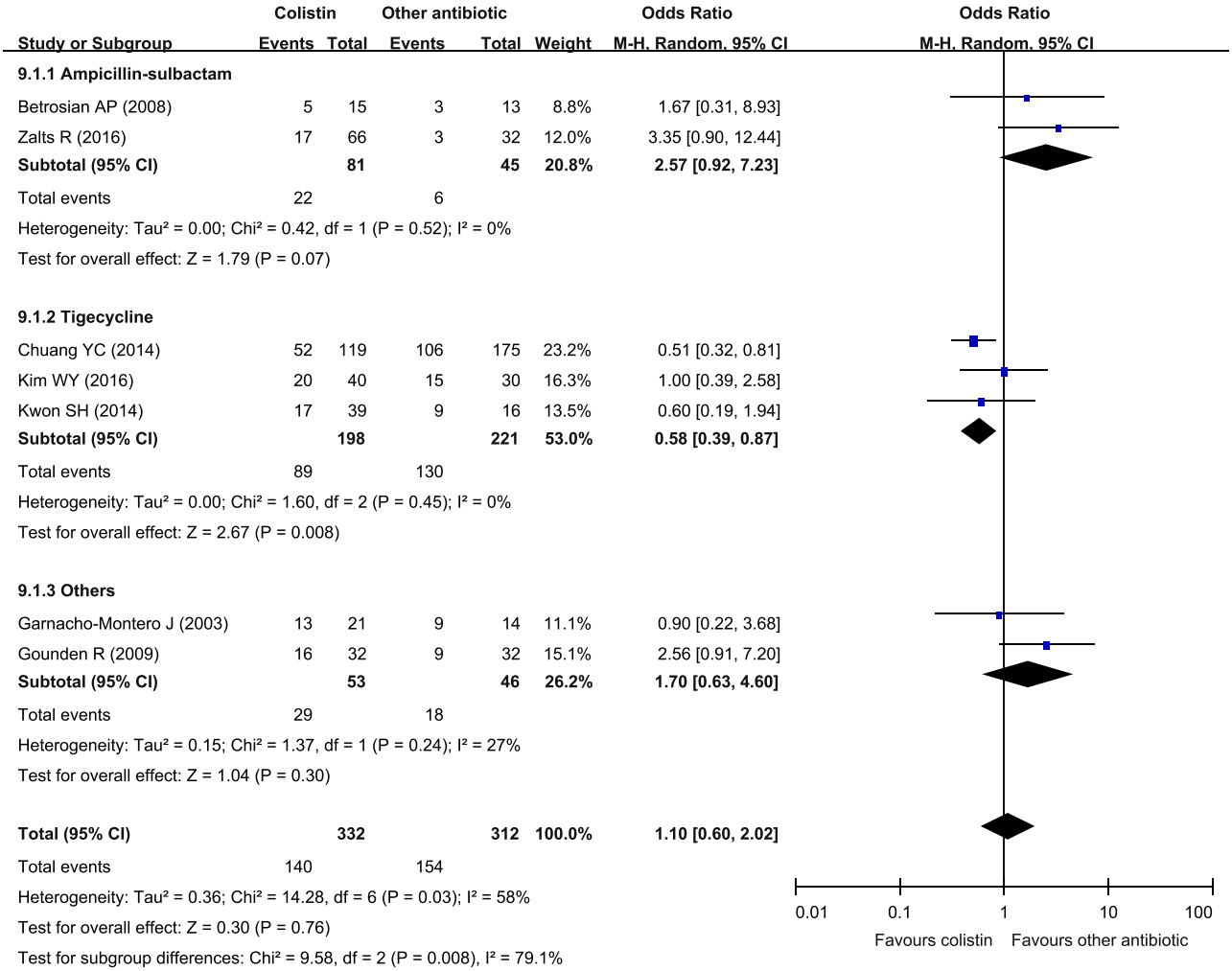
Fig. 3. Forest plot for microbiological eradication between colistin and other antibiotics. CI, confidence interval.

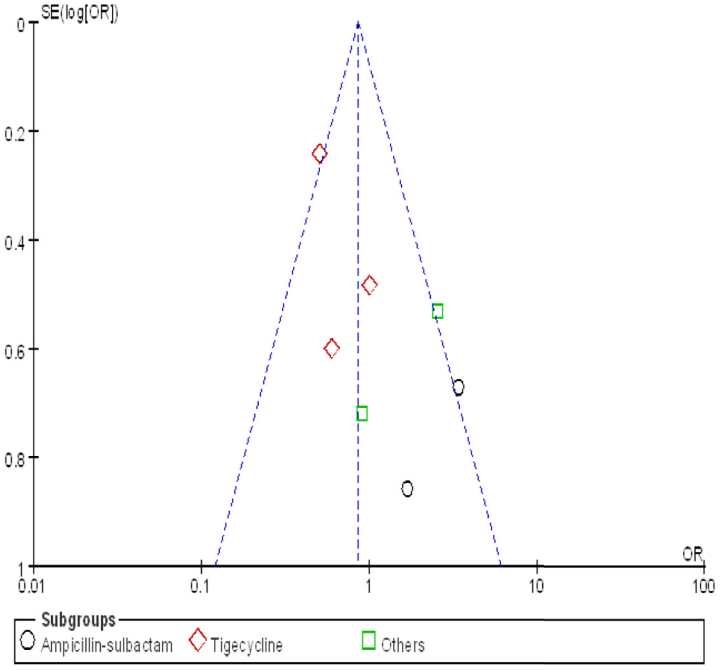




Egger's test results: $t = 1.60$, $p = 0.186$

Fig. 4. Forest plot for nephrotoxicity between colistin and other antibiotics. CI, confidence interval.





Egger test results: $t = 3.5$, $p = 0.017$

Fig. 5. Forest plot for mortality between colistin and other antibiotics. CI, confidence interval.

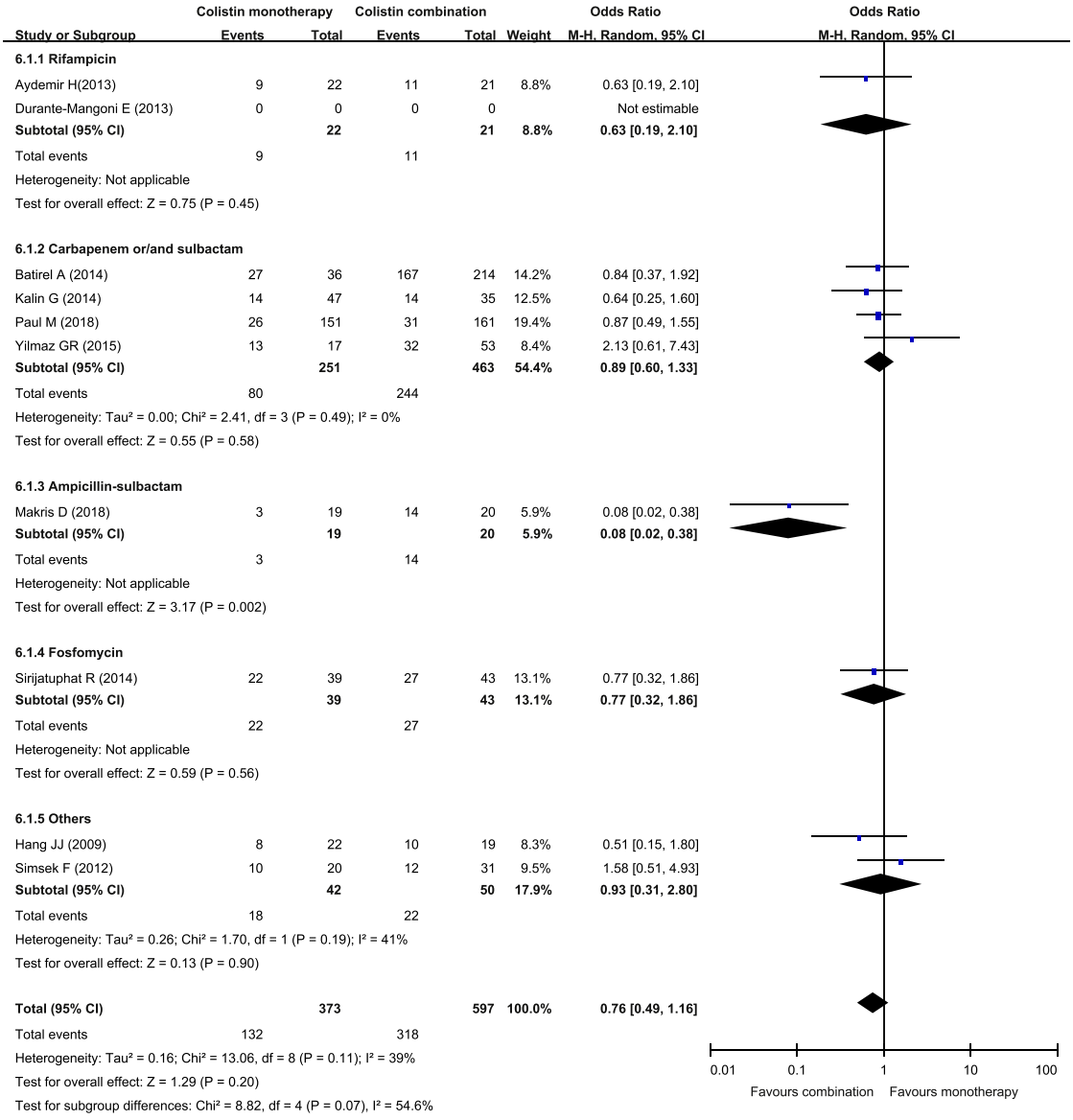
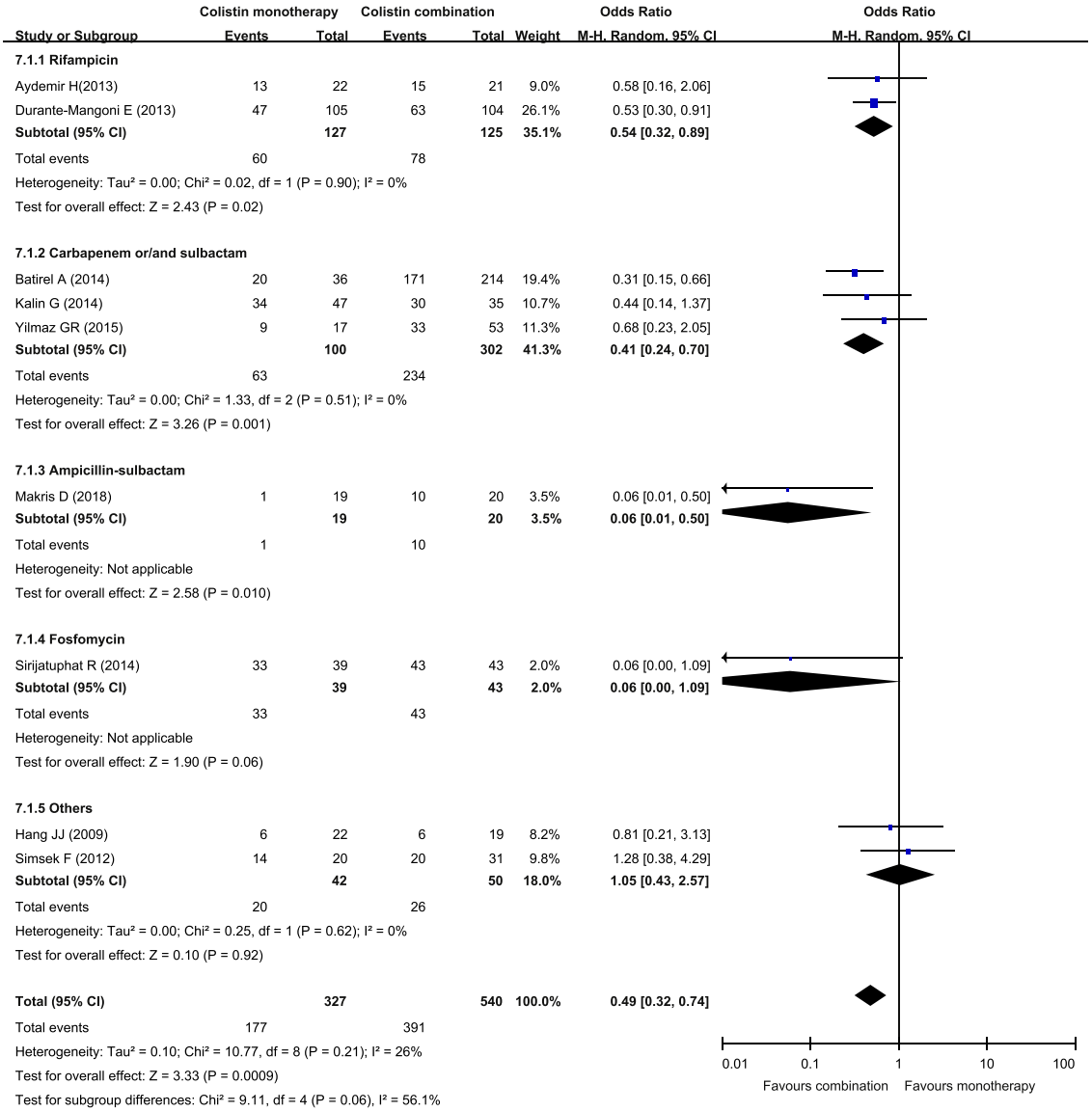
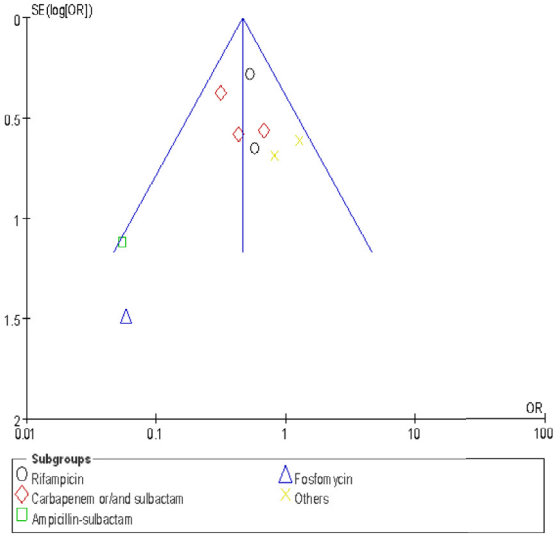


Fig. 6. Forest plot for clinical success between colistin monotherapy and colistin-based combination therapy. CI, confidence interval.

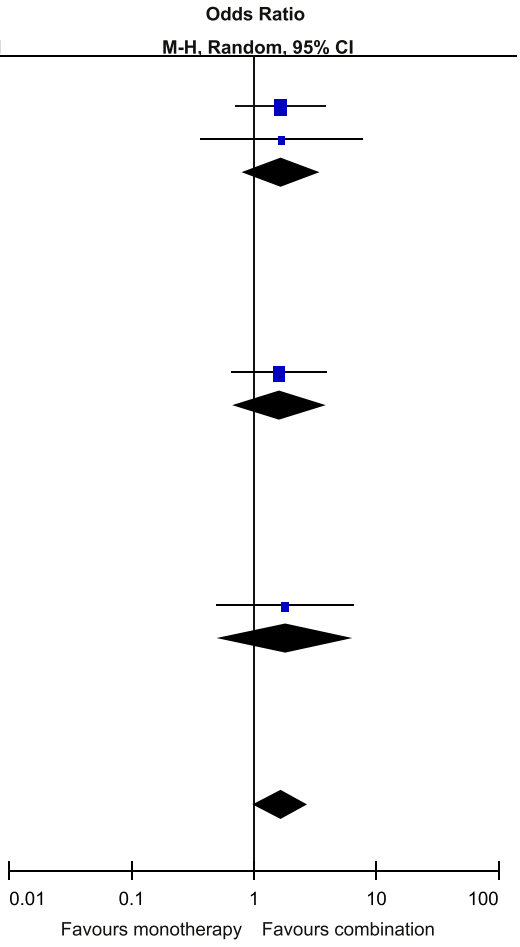


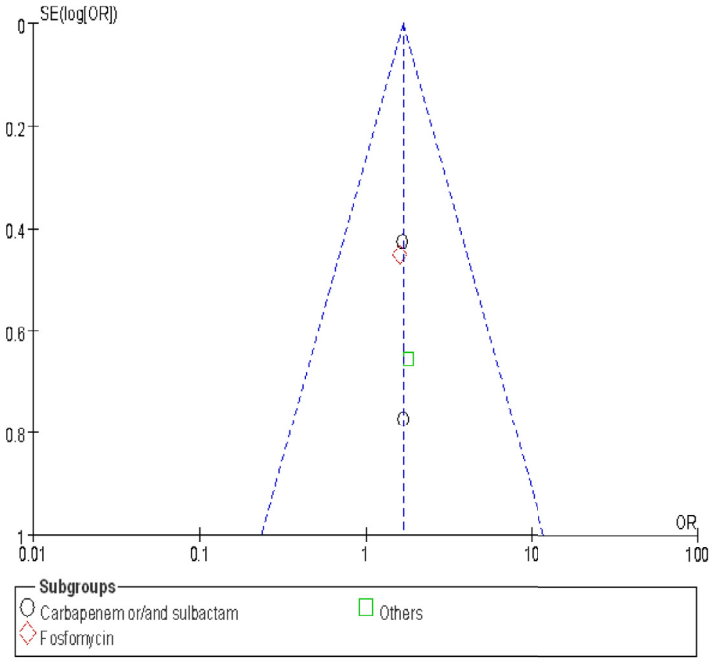


Egger's test results: $t = -1.08$, $p = 0.317$

Fig. 7. Forest plot for microbiological eradication between colistin monotherapy and colistin-based combination therapy. CI, confidence interval.

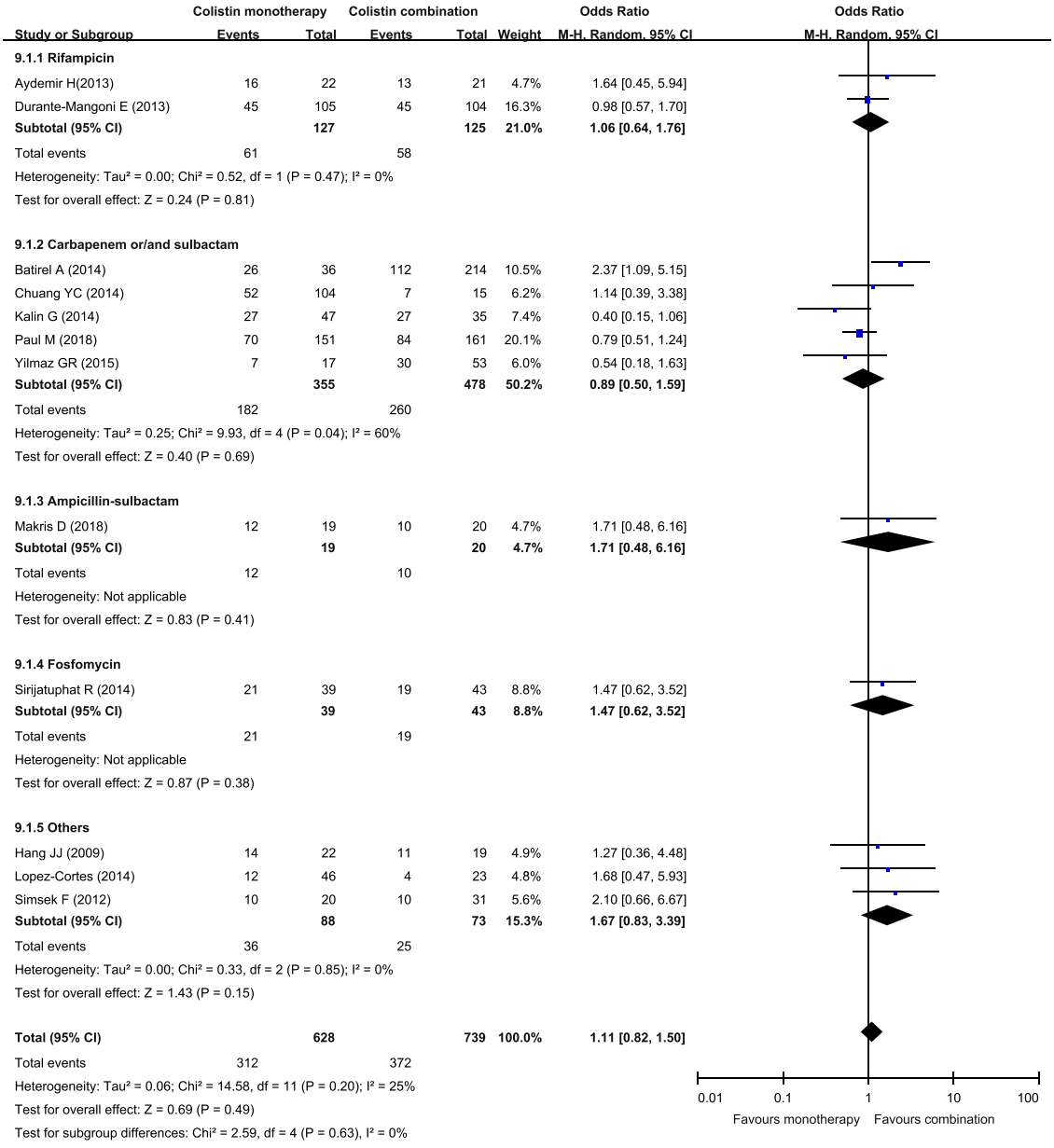
Study or Subgroup	monotherapy Events	Total	combination therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
8.1.1 Carbapenem or/and sulbactam						
Batirel A (2014)	9	36	36	214	38.0%	1.65 [0.72, 3.80]
Yilmaz GR (2015)	3	17	6	53	11.6%	1.68 [0.37, 7.59]
Subtotal (95% CI)		**53**		**267**	**49.7%**	**1.66 [0.80, 3.44]**
Total events	12		42			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.35 (P = 0.18)						
8.1.2 Fosfomycin						
Sirijatuphat R (2014)	19	39	16	43	34.2%	1.60 [0.66, 3.87]
Subtotal (95% CI)		**39**		**43**	**34.2%**	**1.60 [0.66, 3.87]**
Total events	19		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
8.1.3 Others						
Hang JJ (2009)	10	22	6	19	16.2%	1.81 [0.50, 6.50]
Subtotal (95% CI)		**22**		**19**	**16.2%**	**1.81 [0.50, 6.50]**
Total events	10		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**114**		**329**	**100.0%**	**1.66 [0.99, 2.78]**
Total events	41		64			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 3 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Chi² = 0.02, df = 2 (P = 0.99), I² = 0%						

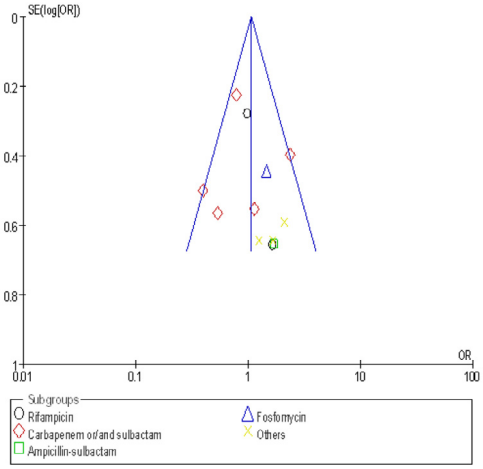




Egger's test results: $t = 1.65$, $p = 0.241$

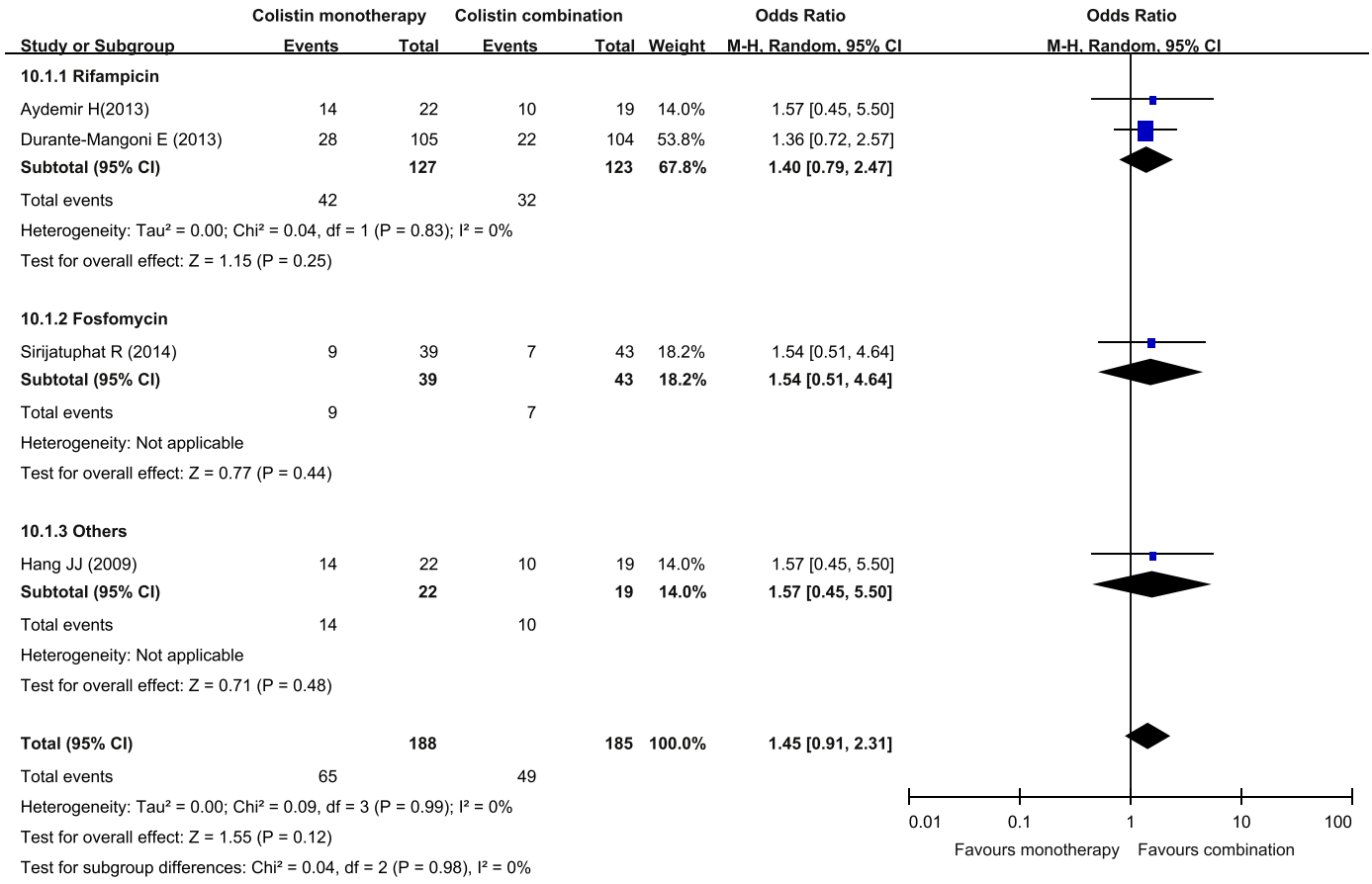
Fig. 8. Forest plot for nephrotoxicity between colistin monotherapy and colistin-based combination therapy. CI, confidence interval.

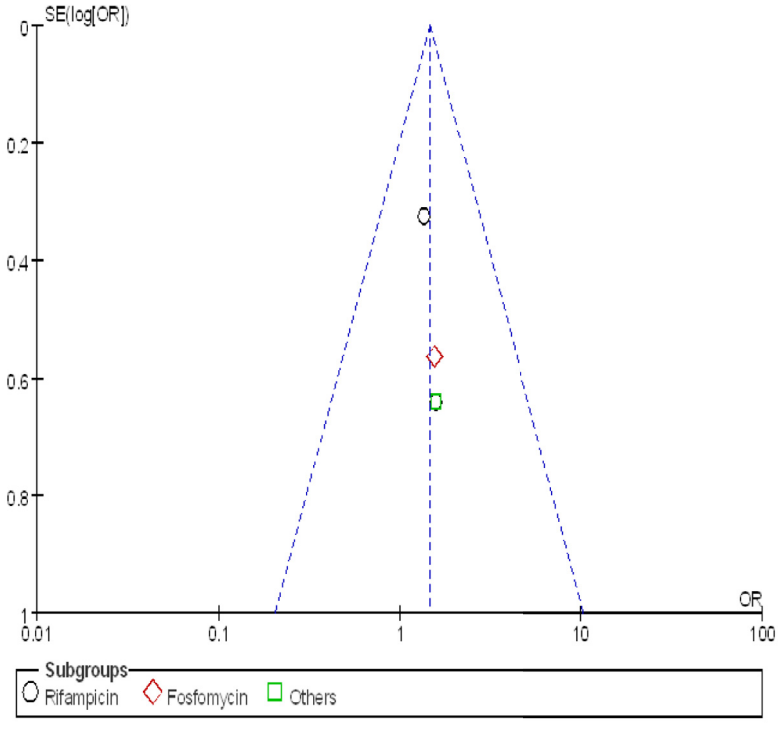




Egger test results: $t = 0.73$, $p = 0.482$

Fig. 9. Forest plot for >28-days or hospital mortality between colistin monotherapy and colistin-based combination therapy. CI, confidence interval.





Egger's test results: $t = 0.87$, $p = 0.478$

Fig. 10. Forest plot for intensive care unit (ICU)-, ventilator-associated pneumonia (VAP)- or infection-related mortality between colistin monotherapy and colistin-based combination therapy. CI, confidence interval.

the colistin treatment group [38]. Nephrotoxicity is generally considered to be a predictor of mortality [39]. However, the current meta-analysis only showed increased nephrotoxicity with the colistin regimen, whilst the mortality of colistin was not higher than other antibiotics. The lack of association between nephrotoxicity and mortality might be attributed to the fact that most nephrotoxicity episodes were categorised as risk or injury and not as severe enough to increase the probability of death [40].

Regarding colistin monotherapy versus colistin-based combination therapy, the current meta-analysis of 12 controlled studies (4 RCTs, 2 prospective and 6 retrospective cohort studies) observed a trend of higher clinical efficacy with colistin-based combination therapy without significant difference. Microbiological eradication in the combination group was significantly higher than with colistin alone. Meanwhile, >28-day mortality did not differ. With double the included studies (12 vs. 6) and patients (1386 vs. 661), the current results are basically consistent with the previous meta-analysis by Chen et al. [12], which also demonstrated similar clinical efficacy and mortality, whilst microbiological eradication favoured the combination group. It is always controversial whether or not colistin combination therapy is more effective than colistin monotherapy. Numerous in vitro studies have shown that colistin combined with another antibiotic exerts synergism against *A. baumannii* [41–47]. However, some clinical studies have reported that combination therapy did not provide any significant advantage compared with colistin alone [25]. The current result is consistent with a recently published network meta-analysis by Kengkla et al. that compared and ranked the efficacy of different colistin combination regimen in patients with MDR and extensively drug-resistant *A. baumannii* infections [48]. Their network meta-analysis included relevant studies published before 18 April 2016. The results indicated that triple therapy with colistin, sulbactam and tigecycline had the highest clinical cure rate, although there were no statistically significant differences between treatment options. Meanwhile, colistin in combination with sulbactam was associated with a significantly higher microbiological cure rate compared with colistin in combination with tigecycline and colistin monotherapy. Nevertheless, although the microbiological eradication results support colistin combination therapy, the bias brought by the different sample collection techniques, sample time and uncertain medical value of the persistence of *A. baumannii* in cultures should not be neglected. Chen et al. did not provide nephrotoxicity results between colistin alone and colistin combination therapy in their meta-analysis [12]. Kengkla et al. found that colistin in combination with other antibiotics was associated with an insignificantly lower risk of nephrotoxicity compared with colistin monotherapy [48]. In contrast to these previously published studies, the current study showed that the incidence of nephrotoxicity was lower in the combination group. It is a little confusing because the dose of colistin in the combination group is the same as the dose in colistin the monotherapy group as indicated in the included studies. This may be attributed to the fact that only four studies were included in the nephrotoxicity meta-analysis and the definitions of nephrotoxicity in these studies were either not completely consistent or were not provided at all. Although the results here are not sufficient to conclude that combination therapy can reduce nephrotoxicity, they at least indicate that combination therapy does not increase the risk of colistin nephrotoxicity. In March 2018, a joint Working Party of the British Society for Antimicrobial Chemotherapy (BSAC), the Healthcare Infection Society (HIS) and the British Infection Association (BIA) issued guidance on the treatment of infections caused by MDR Gram-negative bacteria [49]. The guidance conditionally recommended intravenous colistin for infections due to MDR but polymyxin-susceptible bacteria, preferably in combination with other agents. The current results also support this recommendation.

There are two limitations that should be taken into consideration when interpreting the results of this meta-analysis. First, only four RCTs were included in the meta-analysis, whilst the other 14 studies were retrospective or prospective observational studies. Although almost all of these observational studies stated that there was no significant difference in baseline characteristics between groups, owing to the inherent nature of observational studies, selection bias and confounding is inevitable. Second, this study showed only that microbiological eradication of combination therapy was significantly higher than monotherapy. However, we cannot do further research regarding whether combination therapy can prevent mutation of the pathogen or bring extra selective pressure on the ICU flora, because most of the studies did not report colistin resistance development during colistin-based therapy.

In conclusion, the current meta-analysis found that colistin monotherapy results in a similar clinical response, microbiological response and mortality compared with other antibiotics. However, it did cause more incidences in terms of nephrotoxicity. With a comparable mortality profile to colistin monotherapy, colistin-based combination therapy demonstrated microbiological benefit and no greater risk of nephrotoxicity. Therefore, colistin combination therapy is also one of the options for *A. baumannii* infections. However, as these findings largely relied on data from observational studies, selection bias seems unavoidable, and high-quality RCTs with the results of colistin resistance development are still needed to confirm the beneficial role of colistin combination therapy in the treatment of *A. baumannii* infections.

Funding

This research was supported by the National Natural Science Foundation of China [nos. 81573472 and 81770004].

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Antunes LC, Visca P, Towner KJ. *Acinetobacter baumannii*: evolution of a global pathogen. Pathog Dis 2014;71:292–301.
[2] Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clin Infect Dis 2006;42:657–68.
[3] World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva, Switzerland: WHO; 2017 http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/ accessed 8 February 2019.
[4] Michalopoulos A, Falagas ME. Treatment of *Acinetobacter* infections. Expert Opin Pharmacother 2010;11:779–88.
[5] Potron A, Poirel L, Nordmann P. Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: mechanisms and epidemiology. Int J Antimicrob Agents 2015;45:568–85.
[6] Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538–82.
[7] Pogue JM, Mann T, Barber KE, Kaye KS. Carbapenem-resistant *Acinetobacter baumannii*: epidemiology, surveillance and management. Expert Rev Anti Infect Ther 2013;11:383–93.
[8] Viehman JA, Nguyen MH, Doi Y. Treatment options for carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii* infections. Drugs 2014;74:1315–33.
[9] Huttner B, Jones M, Rubin MA, Neuhauser MM, Gundlapalli A, Samore M. Drugs of last resort? The use of polymyxins and tigecycline at US Veterans Affairs medical centers, 2005–2010. PLoS One 2012;7:e36649.
[10] Xie R, Zhang XD, Zhao Q, Peng B, Zheng J. Analysis of global prevalence of antibiotic resistance in *Acinetobacter baumannii* infections disclosed a faster increase in OECD countries. Emerg Microbes Infect 2018;7:31.

[11] Nowak J, Zander E, Stefanik D, Higgins PG, Roca I, Vila J, et al. High incidence of pandrug-resistant *Acinetobacter baumannii* isolates collected from patients with ventilator-associated pneumonia in Greece, Italy and Spain as part of the MagicBullet clinical trial. J Antimicrob Chemother 2017;72:3277–82.
[12] Chen Z, Chen Y, Fang Y, Wang X, Chen Y, Qi Q, et al. Meta-analysis of colistin for the treatment of *Acinetobacter baumannii* infection. Sci Rep 2015;5:17091.
[13] Nakwan N, Wannaro J, Thongmak T, Pornladnum P, Saksawad R, Nakwan N, et al. Safety in treatment of ventilator-associated pneumonia due to extensive drug-resistant *Acinetobacter baumannii* with aerosolized colistin in neonates: a preliminary report. Pediatr Pulmonol 2011;46:60–6.
[14] Cai Y., Wang R., Wang J. Safety and efficacy of colistin alone or in combination in adults with *Acinetobacter baumannii* infection: a systematic review and meta-analysis. PROSPERO 2018 CRD42018093531. http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018093531 [accessed 8 February 2019].
[15] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.
[16] Nikonova V.S., Kashirskaya N.Y., Kapranov N.I. Efficacy and safety of tobramycin and colistin for inhalation in children with cystic fibrosis from Moscow region. J Cyst Fibros 2010:S54 [abstract no. 210].
[17] Cheng A, Chuang YC, Sun HY, Sheng WH, Yang CJ, Liao CH, et al. Excess mortality associated with colistin–tigecycline compared with colistin–carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: a multicenter prospective observational study. Crit Care Med 2015;43:1194–204.
[18] Chaari A, Pham T, Mnif B, Chtara K, Medhioub F, Baccouche N, et al. Colistin–tigecycline versus colistin–imipenem–cilastatin combinations for the treatment of *Acinetobacter baumannii* ventilator-acquired pneumonia: a prognosis study. Intensive Care Med 2015;41:2018–19.
[19] Kwon SH, Ahn HL, Han OY, La HO. Efficacy and safety profile comparison of colistin and tigecycline on the extensively drug resistant *Acinetobacter baumannii*. Biol Pharm Bull 2014;37:340–6.
[20] Kim WY, Moon JY, Huh JW, Choi SH, Lim CM, Koh Y, et al. Comparable efficacy of tigecycline versus colistin therapy for multidrug-resistant and extensively drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients. PLoS One 2016;11:e0150642.
[21] Hang JJ, Kim MN, Lee K, Hong SB, Lim CM, Koh Y. The comparative efficacy of colistin monotherapy and combination therapy based on in vitro antimicrobial synergy in ventilator-associated pneumonia caused by multi-drug resistant *Acinetobacter baumannii*. Tuberc Respir Dis (Seoul) 2009;67:212–20.
[22] Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2014;58:5598–601.
[23] Chuang YC, Cheng CY, Sheng WH, Sun HY, Wang JT, Chen YC, et al. Effectiveness of tigecycline-based versus colistin-based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis. BMC Infect Dis 2014;14:102.
[24] Zalts R, Neuberger A, Hussein K, Raz-Pasteur A, Geffen Y, Mashiach T, et al. Treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: retrospective comparison between intravenous colistin and intravenous ampicillin–sulbactam. Am J Ther 2016;23:e78–e85.
[25] Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis 2018;18:391–400.
[26] Simsek F, Gedik H, Yildirmak MT, Iris NE, Turkmen A, Ersoy A, et al. Colistin against colistin-only-susceptible *Acinetobacter baumannii*-related infections: monotherapy or combination therapy? Indian J Med Microbiol 2012;30:448–52.
[27] Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Epidemiol Infect 2013;141:1214–22.
[28] Batirel A, Balkan II, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections. Eur J Clin Microbiol Infect Dis 2014;33:1311–22.
[29] Kalin G, Alp E, Akin A, Coskun R, Doganay M. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Infection 2014;42:37–42.
[30] Yilmaz GR, Guven T, Guner R, Kocak Tufan Z, Izdes S, Tasyaran MA, et al. Colistin alone or combined with sulbactam or carbapenem against *A. baumannii* in ventilator-associated pneumonia. J Infect Dev Ctries 2015;9:476–85.
[31] Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar AE, Garcia-Garmendia JL, Bernabeu-Wittel IM, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis 2003;36:1111–18.
[32] Lopez-Cortes LE, Cisneros JM, Fernandez-Cuenca F, Bou G, Tomas M, Garnacho–Montero J, et al. Monotherapy versus combination therapy for sepsis due to multidrug-resistant *Acinetobacter baumannii*: analysis of a multicentre prospective cohort. J Antimicrob Chemother 2014;69:3119–26.
[33] Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Infect 2008;56:432–6.
[34] Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzarlis K, Apostolopoulou O, et al. Colistin versus colistin combined with ampicillin–sulbactam for multiresistant *Acinetobacter baumannii* ventilator-associated pneumonia treatment: an open-label prospective study. Indian J Crit Care Med 2018;22:67–77.
[35] Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, 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.
[36] Gounden R, Bamford C, van Zyl-Smit R, Cohen K, Maartens G. Safety and effectiveness of colistin compared with tobramycin for multi-drug resistant *Acinetobacter baumannii* infections. BMC Infect Dis 2009;9:26.
[37] Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care 2006;10:R27.
[38] Aggarwal R, Dewan A. Comparison of nephrotoxicity of colistin with polymyxin B administered in currently recommended doses: a prospective study. Ann Clin Microbiol Antimicrob 2018;17:15.
[39] Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. a cohort analysis. JAMA 1996;275:1489–94.
[40] Vardakas KZ, Falagas ME. Colistin versus polymyxin B for the treatment of patients with multidrug-resistant Gram-negative infections: a systematic review and meta-analysis. Int J Antimicrob Agents 2017;49:233–8.
[41] Cai X, Yang Z, Dai J, Chen K, Zhang L, Ni W, et al. Pharmacodynamics of tigecycline alone and in combination with colistin against clinical isolates of multidrug-resistant *Acinetobacter baumannii* in an in vitro pharmacodynamic model. Int J Antimicrob Agents 2017;49:609–16.
[42] Lenhard JR, Nation RL, Tsuji BT. Synergistic combinations of polymyxins. Int J Antimicrob Agents 2016;48:607–13.
[43] Lertsrisatit Y, Santimaleeworagun W, Thunyaharn S, Traipattanakul J. In vitro activity of colistin mono- and combination therapy against colistin-resistant *Acinetobacter baumannii*, mechanism of resistance, and clinical outcomes of patients infected with colistin-resistant *A. baumannii* at a Thai university hospital. Infect Drug Resist 2017;10:437–43.
[44] Liu X, Zhao M, Chen Y, Bian X, Li Y, Shi J, et al. Synergistic killing by meropenem and colistin combination of carbapenem-resistant *Acinetobacter baumannii* isolates from Chinese patients in an in vitro pharmacokinetic/pharmacodynamic model. Int J Antimicrob Agents 2016;48:559–63.
[45] Nepka M, Perivolioti E, Kraniotaki E, Politi L, Tsakris A, Pournaras S. In vitro bactericidal activity of trimethoprim–sulfamethoxazole alone and in combination with colistin against carbapenem-resistant *Acinetobacter baumannii* clinical isolates. Antimicrob Agents Chemother 2016;60:6903–6.
[46] Soudeiha MAH, Dahdouh EA, Azar E, Sarkis DK, Daoud Z. In vitro evaluation of the colistin–carbapenem combination in clinical isolates of *A. baumannii* using the checkerboard, Etest, and time–kill curve techniques. Front Cell Infect Microbiol 2017;7:209.
[47] Wei WJ, Yang HF. Synergy against extensively drug-resistant *Acinetobacter baumannii* in vitro by two old antibiotics: colistin and chloramphenicol. Int J Antimicrob Agents 2017;49:321–6.
[48] Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis. J Antimicrob Chemother 2018;73:22–32.
[49] Hawkey PM, Warren RE, Livermore DM, McNulty CAM, Enoch DA, Otter JA, et al. Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. J Antimicrob Chemother 2018;73(Suppl 3):iii2–iii78.