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Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: A systematic review and meta-analysis

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ABSTRACT

Ventilator-associated pneumonia (VAP) caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) has emerged as an important and intractable clinical problem. This review assessed the efficacy and safety of colistin for treatment of MDR GNB VAP. PubMed and Embase were searched for controlled studies of colistin for treatment of MDR GNB VAP. The Mantel–Haenszel random-effects model was used to pool odds ratios (ORs) with 95% confidence intervals (CIs). The primary outcome was clinical cure; secondary outcomes were microbiological eradication, ICU mortality, hospital mortality, length of ICU stay and nephrotoxicity. Fourteen controlled studies involving 1167 patients were identified, including six reporting colistin versus β-lactam antibiotics, three reporting aerosolised (AS) plus intravenous (IV) colistin versus IV colistin alone and five reporting colistin combined therapy versus colistin monotherapy. The clinical cure rate of colistin was comparable with that of β-lactam antibiotics (OR = 1.00, 95% CI 0.68–1.47). Compared with IV colistin alone, AS plus IV colistin exhibited a better clinical cure (OR = 2.12, 95% CI 1.40–3.20). Compared with colistin monotherapy, colistin combined therapy did not appear to provide a better clinical cure (OR = 1.38, 95% CI 0.81–2.33). There was no significant difference in nephrotoxicity and other secondary outcomes between the treatment groups. Colistin appears as effective and safe as β-lactam antibiotics for the treatment of MDR GNB VAP. AS colistin may be a beneficial adjunct to IV colistin in the management of MDR GNB VAP. Colistin combined therapy does not appear to provide better outcomes compared with colistin monotherapy.

1. Introduction

Ventilator-associated pneumonia (VAP) remains the most common nosocomial infection in the intensive care unit (ICU) setting, affecting 8–28% of patients receiving mechanical ventilation [1], markedly increasing mortality and prolonging the length of ICU stay, especially when the episode of VAP is caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) [2,3]. Increasing multidrug resistance in GNB, in particular *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, represents one of the most serious clinical problems confronted by intensive care clinicians. In the last two decades, the paucity of novel antibiotics has forced clinicians to reconsider some 'old' antibiotics such as the polymyxins, most commonly colistin (polymyxin E) [4].

Although most recent studies [5–8] suggest that colistin is an effective and safe antimicrobial agent for MDR GNB VAP, there are still many unsolved problems that require further investigation. For example, undocumented drug dosage regimens may lead to inappropriate and indiscriminate clinical use of colistin. Meanwhile, what is worth paying more attention to is whether addition of aerosolised (AS) colistin to intravenous (IV) colistin can improve the outcome of treatment of MDR GNB VAP compared with IV colistin alone. In addition, it remains unknown whether colistin combined therapy can provide a better outcome than colistin monotherapy for the treatment of MDR GNB VAP. In light of these questions, a systematic review and meta-analysis of current evidence was performed to investigate the efficacy and safety of colistin versus β-lactam antibiotics, of AS plus IV colistin versus IV colistin alone, and of colistin combined therapy versus colistin monotherapy for the treatment of MDR GNB VAP.

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2. Methods

2.1. Search strategy and selection criteria

To ensure that all relevant studies were captured, PubMed and Embase databases were searched, starting from their inception, without any restriction on language, publication date, study design or study quality. ClinicalTrials.gov (http://ClinicalTrials.gov) was also searched. Search terms were combined as follows: ('colistin' OR 'colymycin' OR 'colistimethate' OR 'polymixin E') AND ('VAP' OR 'ventilator-associated pneumonia'). Two independent investigators (WJG and FW) carried out the initial search, deleted duplicate records, screened the titles and abstracts for relevance, and then identified studies as included, excluded or requiring further assessment. The last search was run in March 2014. References of the retrieved articles and previous reviews were also checked manually to identify additional potentially eligible studies. Discrepancies were resolved by discussion between the two investigators.

All controlled studies were included if they investigated the efficacy of colistin for the treatment of MDR GNB VAP in adult patients. Considering the low number of randomised controlled trials (RCTs) on this subject, no predefined limitations on study design or study quality were applied. RCTs, cohort studies and case-control studies were all included.

2.2. Data extraction and quality assessment

Data extraction was performed by WJG and was confirmed independently by FW. The following information was extracted from each study: first author; year of publication; country; study design; patient characteristics; number of patients enrolled; infecting organisms of MDR GNB VAP; total daily dose of AS colistin and/or IV colistin; susceptibility testing for colistin and other antibiotics; definition of VAP; and outcome data (clinical cure, microbiological eradication, ICU mortality, hospital mortality, length of ICU stay and nephrotoxicity). Extracted data were entered into a standardised Excel file (Microsoft Corp., Redmond, WA). Discrepancies were resolved by discussion between the two investigators. RCTs were appraised for methodological quality using the Jadad score [9]. The nine-star Newcastle–Ottawa Scale was used to assess the quality of non-randomised observational studies [10].

2.3. Outcome variables and definitions

The primary outcome was clinical cure, and secondary outcomes included microbiological eradication, ICU mortality, hospital mortality, length of ICU stay and nephrotoxicity. Clinical cure was defined as resolution of symptoms and signs of VAP, with or without an improvement or lack of significant progression of radiographic findings by the end of therapy. Microbiological eradication was defined as negative culture of specimens at the end of treatment, regardless of the clinical outcome. In patients with normal renal function, nephrotoxicity was defined as a serum creatinine value >2 mg/dL, as a 50% reduction in the calculated creatinine clearance compared with the baseline value, or as a need for renal replacement therapy. In patients with pre-existing renal dysfunction, nephrotoxicity was defined as a 50% increase in the baseline creatinine level, as a 50% reduction in the calculated creatinine clearance compared with the baseline value, or as a need renal replacement therapy.

2.4. Statistical analysis

Differences were expressed as odds ratio (OR) with 95% confidence intervals (CI) for dichotomous outcomes, and as weighted mean difference (WMD) with 95% CI for continuous outcomes. The Mantel–Haenszel random-effects model was used to calculate pooled ORs or WMDs with 95% CIs [11]. Heterogeneity across studies was measured by I^2 statistics examining the percentage of heterogeneity due to variation between studies. An I^2 value >50% indicates significant heterogeneity. Publication bias was not assessed because the pooled estimate included fewer than ten trials [12]. A two-tailed P-value of <0.05 was considered significant except where a certain P-value had been given. All statistical analyses were performed using RevMan software v.5.2 (The Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Study selection

The selection process is shown in Fig. 1. The initial database search yielded 571 records, of which 112 records were excluded as duplicates and 443 records were excluded based on the titles and abstracts for various reasons (reviews, letters, case reports, case series or irrelevance to the analysis). The remaining 16 full-text articles were assessed for eligibility, 3 of which were also excluded because one focused on paediatric patients [13], one compared colistin with normal saline rather than standard antibiotics [14] and one reported inadequate allocation resulting in a significant potential for selection bias [15]. Finally, 13 articles [5–8,16–24] were included in the meta-analysis. As one article [16] contained two studies investigating the efficacy of colistin versus β-lactam antibiotics and of colistin combined therapy with colistin monotherapy for treating MDR GNB VAP, respectively, a total of 14 eligible studies met all the inclusion criteria and were included in the meta-analysis.

3.2. Study characteristics

The study characteristics are presented in Table 1. The studies spanned from 2003 to 2013. The sample size ranged from 28 to 208 (total 1167). Of the 14 included studies, 2 were RCTs [8,23], 4 were case-control studies [6,18,20,22] and 8 were cohort studies [5,7,16,17,19,21,24]. Six studies compared colistin with β-lactam antibiotics [5–8,16,17], three studies compared AS plus IV colistin with IV colistin alone [18–20] and five studies compared colistin combined therapy with colistin monotherapy [16,21–24]. All 14 included studies reported clinical cure events [5–8,16–24], 9 reported microbiological eradication events [5,8,17,18,20–24], 8 reported ICU mortality events [5,6,16,18–21,24], 6 reported hospital mortality events [5–7,19,21,23], 7 reported length of ICU stay [5,6,8,17,21,23,24] and 8 reported nephrotoxicity [5,7,8,16–18,20,21].

3.3. Colistin versus β-lactam antibiotics

Six studies compared colistin with β-lactam antibiotics for the treatment of MDR GNB VAP [5–8,16,17]. The clinical cure rate of colistin was comparable with that of β-lactam antibiotics (OR = 1.00, 95% CI 0.68–1.47, $P = 0.99$, $I^2 = 0\%$; Fig. 2). There were no significant differences in microbiological eradication (OR = 0.64, 95% CI 0.18–2.22, $P = 0.48$, $I^2 = 38\%$; Fig. 3), ICU mortality (OR = 1.02, 95% CI 0.60–1.72, $P = 0.95$, $I^2 = 0\%$; Fig. 4), hospital mortality (OR = 1.17, 95% CI 0.68–2.02, $P = 0.57$, $I^2 = 0\%$; Fig. 5), length of ICU stay (WMD = 0.12 days, 95% CI −3.68 to 3.91, $P = 0.95$, $I^2 = 0\%$; Fig. 6) and nephrotoxicity (OR = 1.26, 95% CI 0.62–2.58, $P = 0.52$, $I^2 = 0\%$; Fig. 7) between the two groups.

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Table 1
Study characteristics.

First author	Year/location	Study design/quality[a]	Population	No. of patients	Infecting organism	Intervention	Colistin regimen	
Colistin versus β-lactam antibiotics								
Garnacho-Montero et al. [5]	2003/Spain	PC/9	Adult ICU patients with MDR VAP	35 (21/14)	*Acinetobacter baumannii*	IV colistin	IV imipenem/cilastatin	Adjusted for renal function[b]
Kallel et al. [6]	2007/Tunisia	CC/9	Adult ICU patients with PDR VAP	120 (60/60)	*A. baumannii*, *Pseudomonas aeruginosa*	IV colistin	IV imipenem/cilastatin	6 MIU/day divided into three doses for 14 days
Rios et al. [7]	2007/Argentina	RC/7	Adult ICU patients with MDR VAP	61 (31/30)	*A. baumannii*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*	IV colistin	IV imipenem/cilastatin	5 mg/kg/day for 14 days, doses were corrected in patients with renal failure[c]
Betrosian et al. [8]	2008/Greece	RCT/3	Adult ICU patients with MDR VAP	28 (15/13)	*A. baumannii*	IV colistin	IV ampicillin/sulbactam	9 MIU/day divided into three doses for 8–10 days
Lu et al. [16]	2012/France	PC/8	Adult ICU patients with MDR VAP	165 (43/122)	*A. baumannii*, *P. aeruginosa*	AS colistin	IV β-lactam	6 MIU/day divided into three doses for 14 days or until successful weaning from mechanical ventilation
Zalts et al. [17]	2013/Israel	RC/8	Adult ICU patients with CR VAP	98 (66/32)	*A. baumannii*	IV colistin	IV ampicillin/sulbactam	6 MIU/day divided into three doses for 7–10 days
AS plus IV colistin versus IV colistin alone								
Kofteridis et al. [18]	2010/Greece	CC/9	Adult ICU patients with MDR VAP	86 (43/43)	*A. baumanii*, *P. aeruginosa*, *K. pneumoniae*	AS + IV colistin	IV colistin	AS: 2 MIU/day divided into two doses IV: 9 MIU/day divided into two doses
Korbila et al. [19]	2010/Greece	RC/7	Adults hospitalised patients with MDR VAP	121 (78/43)	*A. baumanii*, *P. aeruginosa*, *K. pneumoniae*	AS + IV colistin	IV colistin	AS: 2.1 ± 0.9 MIU/day IV: 7.0 ± 2.4 (AS + IV)/6.4 ± 2.3 (IV alone) MIU/day[d]
Tumbarello et al. [20]	2013/Italy	CC/9	Adult ICU patients with COS VAP	208 (104/104)	*A. baumanii*, *P. aeruginosa*, *K. pneumoniae*	AS + IV colistin	IV colistin	AS: 3 MIU/day IV: 7.0 ± 2.6 (AS + IV)/7.3 ± 2.4 (IV alone) MIU/day[d]
Colistin combined therapy versus colistin monotherapy								
Jang et al. [21]	2009/South Korea	RC/8	Adult ICU patients with MDR VAP	41 (19/22)	*A. baumannii*	IV colistin + other IV antibiotics	IV colistin	5 mg/kg/day

Table 1 (*Continued*)

First author	Year/location	Study design/quality[a]	Population	No. of patients	Infecting organism	Intervention	Colistin regimen	
Lu et al. [16]	2012/France	PC/8	Adult ICU patients with MDR VAP	43 (15/28)	*A. baumannii*, *P. aeruginosa*	AS colistin + IV β-lactam	AS colistin	6 MIU/day divided into three doses for 14 days or until successful weaning from mechanical ventilation
Simsek et al. [22]	2012/Turkey	CC/9	Adult hospitalised patients with COS VAP	36 (21/15)	*A. baumannii*	IV colistin + other IV antibiotics	IV colistin	6 MIU/day divided into three doses
Aydemir et al. [23]	2013/Turkey	RCT/3	Adult hospitalised patients with CR VAP	43 (21/22)	*A. baumannii*	IV colistin + nasogastric rifampicin	IV colistin	Adjusted for renal function[e]
Kalin et al. [24]	2013/Turkey	RC/8	Adult ICU patients with MDR VAP	82 (35/47)	*A. baumannii*	IV colistin + IV sulbactam	IV colistin	Adjusted for renal function[f]

PC, prospective cohort; CC, case-control; RC, retrospective cohort; RCT, randomised controlled trial; ICU, intensive care unit; MDR, multidrug-resistant; VAP, ventilator-associated pneumonia; PDR, pan-drug-resistant; CR, carbapenem-resistant; COS, colistin-only susceptible; IV, intravenous; AS, aerosolised; MIU, million international units.

[a] Quality assessment was done using the Newcastle–Ottawa Scale (range 0–9) for non-randomised studies and using a Jadad score (range 0–5) for RCTs.

[b] For patients with normal renal function, the dosage was 2.5–5.0 mg/kg/day divided into three doses. In the serum creatinine level was 1.2–1.5 mg/dL, the dosage administered was 2.5–3.8 mg/kg/day divided into two doses; serum creatinine level of 1.6–2.5 mg/dL, 2 mg/kg/day in one dose; and serum creatinine level ≥2.6 mg/dL, 1.5 mg/kg every 48 h.

[c] If the serum creatinine level was 1.3–1.5 mg/dL, the dosage administered was 2.5–5.0 mg/kg/day; serum creatinine level of 1.6–2.5 mg/dL, 2.5 mg/kg/day; and serum creatinine level >2.5 mg/dL, 1–1.5 mg/kg/day.

[d] Mean ± standard deviation.

[e] For patients with normal renal function, the dosage was 300 mg/day. If the serum creatinine level was 1.3–1.5 mg/dL, the dosage administered was 230 mg/day divided into two doses; serum creatinine level of 1.6–2.5 mg/dL, 150 mg/day in one dose; and serum creatinine level of >2.5 mg/dL, 100 mg every 36 h.

[f] For patients with normal renal function, the dosage was 5 mg/kg/day. For a creatinine clearance (CL_{Cr}) ≥80 mL/min, the dosage administered was 5.0 mg/kg/day; CL_{Cr} 30–79 mL/min, 2.5–3.8 mg/kg/day; and for CL_{Cr} <30 mL/min, 2.5 mg/kg/day. For anuric patients, 2.5 mg/kg every other day after dialysis.

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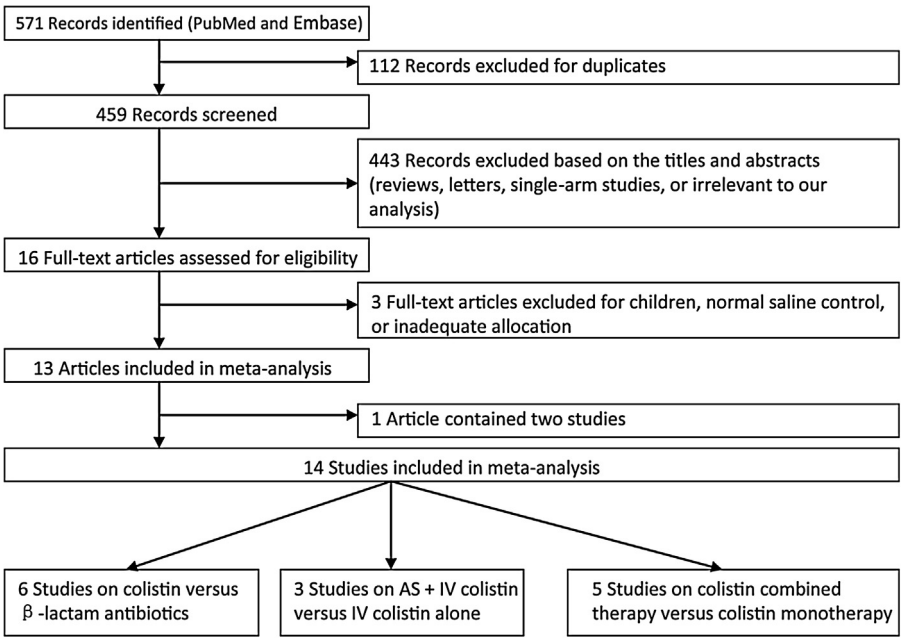

Fig. 1. Flow diagram of the selection process of the included studies. AS, aerosolised; IV, intravenous.

3.4. Aerosolised plus intravenous colistin versus intravenous colistin alone

Three studies compared AS plus IV colistin with IV colistin alone for the treatment of MDR GNB VAP [18–20]. Compared with IV colistin alone, AS plus IV colistin had a higher clinical cure rate (OR = 2.12, 95% CI 1.40–3.20, $P = 0.0004$, $I^2 = 0\%$; Fig. 2). There were no significant differences in microbiological eradication (OR = 1.29, 95% CI 0.63–2.63, $P = 0.48$, $I^2 = 43\%$; Fig. 3), ICU mortality (OR = 0.75, 95% CI 0.50–1.11, $P = 0.15$, $I^2 = 0\%$; Fig. 4), hospital mortality (OR = 0.83, 95% CI 0.39–1.77, $P = 0.63$; Fig. 5) and nephrotoxicity (OR = 1.13, 95% CI 0.65–1.96, $P = 0.67$, $I^2 = 0\%$; Fig. 7) between the two groups.

3.5. Colistin combined therapy versus colistin monotherapy

Five studies compared colistin combined therapy with colistin monotherapy for the treatment of MDR GNB VAP [16,21–24]. Compared with colistin monotherapy, colistin combined therapy did not have a better clinical cure (OR = 1.38, 95% CI 0.81–2.33, $P = 0.23$, $I^2 = 0\%$; Fig. 2). There were no significant differences in microbiological eradication (OR = 1.49, 95% CI 0.79–2.83, $P = 0.22$, $I^2 = 0\%$;

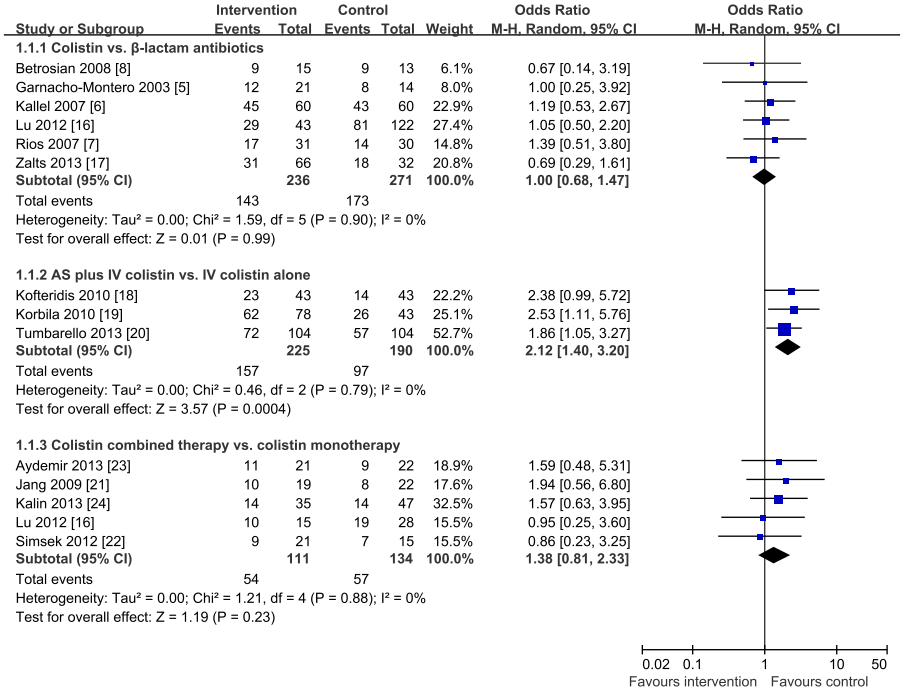

Fig. 2. Forest plot depicting clinical cure. AS, aerosolised; IV, intravenous.

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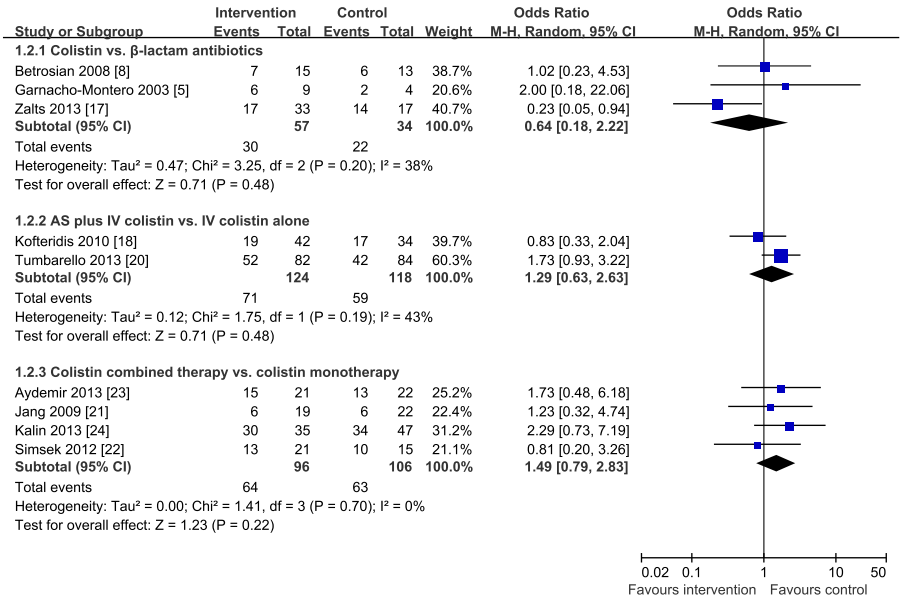

Fig. 3. Forest plot depicting microbiological eradication. AS, aerosolised; IV, intravenous.

Fig. 3), ICU mortality (OR = 0.48, 95% CI 0.22–1.03, $P = 0.06$, $I^2 = 0\%$; Fig. 4), hospital mortality (OR = 0.69, 95% CI 0.28–1.71, $P = 0.43$, $I^2 = 0\%$; Fig. 5), length of ICU stay (WMD = −0.28 days, 95% CI −9.19 to 8.64, $P = 0.95$, $I^2 = 0\%$; Fig. 6) and nephrotoxicity (OR = 0.55, 95% CI 0.15–1.99, $P = 0.37$; Fig. 7) between the two groups.

4. Discussion

This systematic review and meta-analysis of 14 controlled studies provides evidence that colistin is as effective as β-lactam antibiotics for the treatment of MDR GNB VAP, without an increased risk of nephrotoxicity. In addition, AS colistin might be a beneficial adjunct to IV colistin in the management of MDR GNB VAP. However, colistin combined therapy did not appear to provide better outcomes compared with colistin monotherapy.

A previous systematic review evaluating the efficacy and safety of colistin for the treatment of VAP compared with standard antibiotics was published in 2012 [25]. It included six controlled studies for analysis, including four studies described here [5–8], and suggested that colistin may be as safe and efficacious as standard antibiotics for the treatment of VAP. The current analysis did not include two studies that were included in the previous review, because one mainly involved paediatric patients [13] and the other compared solitary colistin with normal saline rather than standard antibiotics [14]. The results of the current meta-analysis suggested that colistin might be as effective as β-lactam antibiotics for the treatment of MDR GNB VAP, without an increased risk of nephrotoxicity. Although consistent, the findings of this meta-analysis generally concur and further reinforce earlier results by including another two recently published and relatively large studies [16,17].

Different from the previous review, this meta-analysis further assessed the role of AS colistin as adjunctive therapy to IV colistin as well as colistin combined therapy in the treatment of MDR GNB VAP. The efficacy of colistin for the treatment of MDR GNB VAP has been questioned because of its inadequate penetration into the lung parenchyma [26]. AS antibiotics have been used to manage MDR

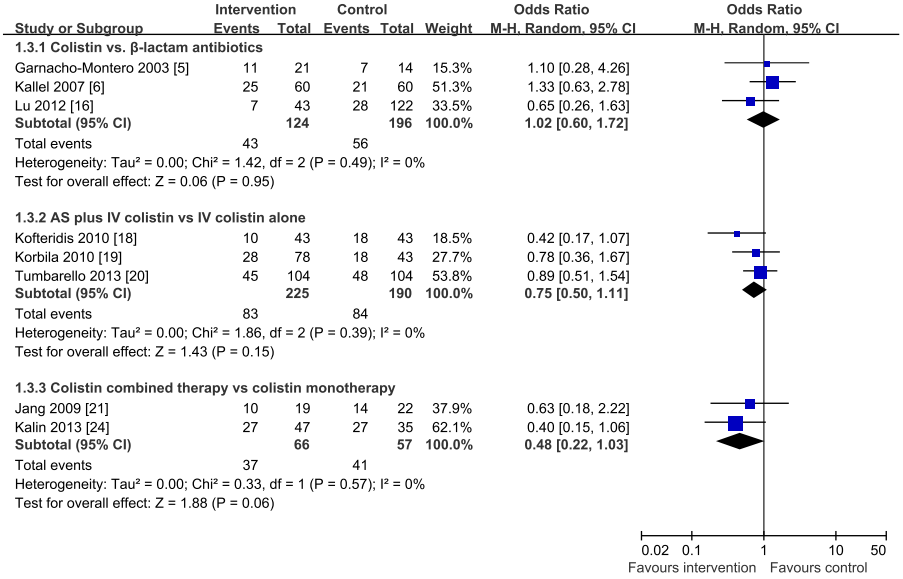

Fig. 4. Forest plot depicting intensive care unit mortality. AS, aerosolised; IV, intravenous.

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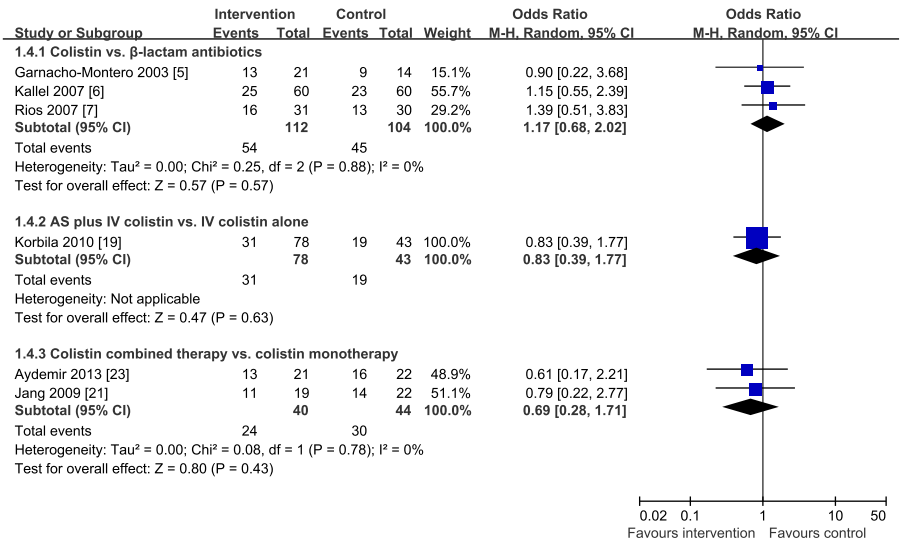

Fig. 5. Forest plot depicting hospital mortality. AS, aerosolised; IV, intravenous.

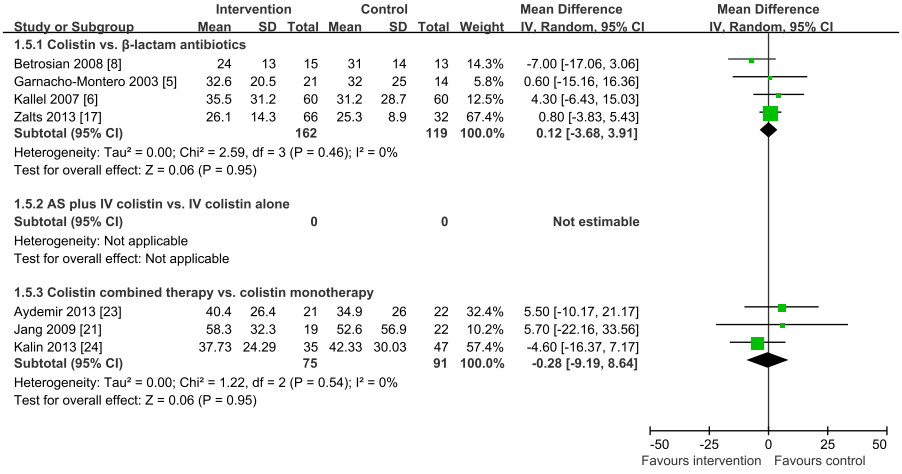

Fig. 6. Forest plot depicting the length of intensive care unit stay. AS, aerosolised; IV, intravenous.

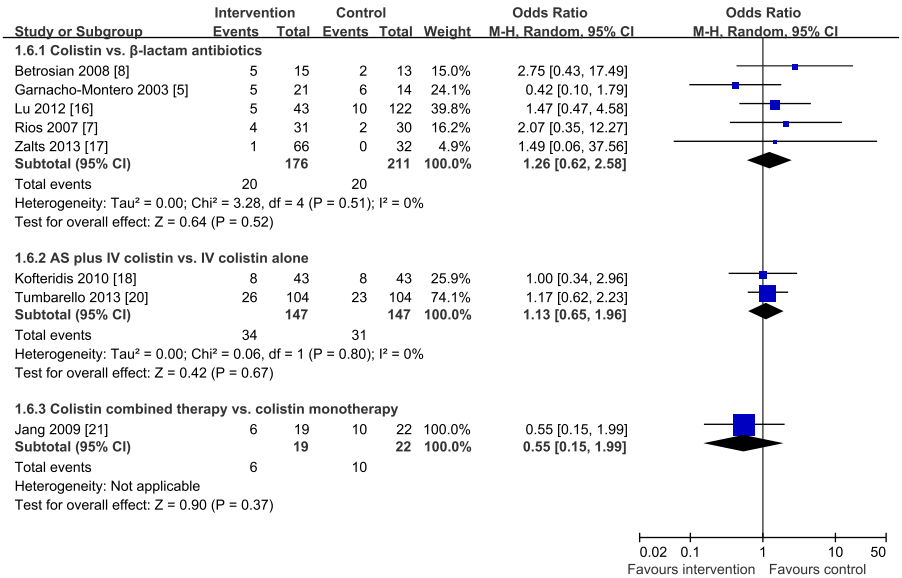

Fig. 7. Forest plot depicting nephrotoxicity. AS, aerosolised; IV, intravenous.

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Table 2
Incidence of nephrotoxicity and other adverse events in included studies.

Study	Nephrotoxicity, No./total (%)	Neurotoxicity, No./total (%)	Other adverse events	Treatment discontinuation
Garnacho-Montero et al. [5]	5/21 (23.8)[a]	None	N/A	None
Kallel et al. [6]	None	N/A	One patient treated with colistin developed diffuse muscular weakness during hospitalisation that resolved within 1 month after ICU discharge	None
Rios et al. [7]	4/31 (12.9)	N/A	N/A	None
Betrosian et al. [8]	5/15 (33.3)	None	N/A	None
Lu et al. [16]	5/43 (11.6)	N/A	N/A	None
Zalts et al. [17]	1/66 (1.5)[b]	N/A	N/A	None
Kofteridis et al. [18]	16/86 (18.6)	None	No adverse events such as bronchoconstriction, apnoea or chest tightness	None
Korbila et al. [19]	N/A	N/A	No adverse events such as bronchoconstriction	None
Tumbarello et al. [20]	49/208 (23.6)	N/A	N/A	None
Jang et al. [21]	16/41 (39.0)	N/A	N/A	None
Simsek et al. [22]	N/A	N/A	N/A	None
Aydemir et al. [23]	10/43 (23.3)	None	N/A	None
Kalin et al. [24]	22/82 (26.8)	N/A	Hepatotoxicity was seen in two patients (5.4%) in the colistin/sulbactam combination group and eight patients (15.4%) in the colistin monotherapy group, with no statistically significant difference	None

N/A, not available; ICU, intensive care unit.
[a] Three patients required dialysis.
[b] Defined as a requirement for haemodialysis.

GNB VAP with encouraging results [27,28]. Given the high morbidity and mortality of MDR GNB VAP, it is important to determine whether AS colistin as adjunctive therapy can improve the efficacy of treatment of MDR GNB VAP. This meta-analysis suggested that addition of AS colistin to IV colistin had a higher clinical cure rate compared with IV colistin alone, probably because AS colistin may produce high drug levels in the lungs, and high drug deposition in the lung tissue facilitates rapid and efficient bacterial killing. Another possible explanation might be that addition of AS colistin to IV colistin brought a higher dose than IV colistin alone, since a higher dosage of colistin for VAP has a higher efficacy [29].

Recent studies suggested that combined treatment with two or more antibiotics may be more effective than active monotherapy against MDR GNB VAP [30,31]. The current meta-analysis suggested that colistin combined therapy did not show better outcomes compared with colistin monotherapy. However, the clinical cure rate and microbiological eradication rate were higher in the colistin combined therapy group than in the colistin monotherapy group (48.6% vs. 42.5% and 66.7% vs. 59.4%, respectively), although the differences were not statistically significant. Our findings suggest that clinicians should consider the combined use of colistin with other antibiotics when treating MDR GNB VAP because it may avoid the emergence and development of colistin resistance [32].

We further assessed the effects of colistin on ICU mortality, hospital mortality and length of ICU stay and found that there were no significant differences between treatment groups. The results were not surprising given that these outcomes may be closely related to other factors such as patient age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and the presence or absence of comorbidity [19,33].

Not unexpectedly, another issue that merits attention is the safety of colistin. Nephrotoxicity is one of the most important factors limiting the use of colistin. As shown in Table 2, the occurrence of nephrotoxicity associated with colistin treatment ranged from 1.5% to 39.0% in the included studies, where no patient discontinued the use of colistin because of this adverse effect. No neurotoxicity or neuromuscular blockade were reported in the patients in these studies. One study [5] evaluated the neurophysiological function in 12 colistin recipients and no evidence of neuromuscular junction blockade was reported, although typical features consistent with critical illness polyneuropathy were seen in ca. 50% of the patients. Kallel et al. [6] reported that one patient treated with colistin developed diffuse muscular weakness during hospitalisation but it resolved within 1 month after ICU discharge. No significant adverse events of AS colistin such as bronchoconstriction were reported by Kofteridis et al. [18] and Korbila et al. [19]. Kalin et al. [24] reported that the occurrence of hepatotoxicity was 5.4% in the colistin/sulbactam combination group and 15.4% in the colistin monotherapy group, with no statistically significant difference.

Several potential limitations should be taken into consideration when interpreting the results. First, among the 14 included studies, only 2 were small RCTs and the other 12 studies were observational studies. Although most of the included observational studies reported that there was no significant difference in the baseline characteristics between groups, observational studies are highly subject to selection bias and confounding by indication in nature. Second, some of the pooled analyses were based on limited evidence and modest sample size. Thus, these comparisons might be vastly underpowered to answer the question of whether there is a potential significant difference between groups. Third, regarding the dosing regimen of colistin, insufficient dosing runs the risk of treatment failure and poor outcomes and potentially increases colistin resistance [34], whilst excessive dosing may be associated with an increased risk of nephrotoxicity [35]. Among the included studies, great variation existed in the dosage of colistin. Moreover, the number of included studies for each outcome is limited. At present, a sensitivity analysis accordingly to dose regimen is unreasonable. The optimal dosing schedule still remains to be explored. Fourth, although colistin combined therapy can provide a better outcome than colistin monotherapy, it is unknown what other preferable antibiotics should be combined with colistin for the treatment of MDR GNB VAP. Finally, recently the US Centers for Disease Control and Prevention (CDC) and the Society of Critical Care Medicine (SCCM) have adopted the concept of ventilator-associated events (VAEs). Before this, only VAP was used in this context. A VAE is diagnosed as deterioration in respiratory status after a period of stability or improvement in combination with signs of infection and positive sputum cultures. As the main difference between VAP and VAE is that a VAE does not require infiltrates/consolidations on a chest radiograph, it will

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be more sensitive but probably not more specific. The new use of VAE is not intended to be used in patient management and this is very different from the use of VAP as clinicians would probably treat all VAP in patients. Caution should be raised whether there is equal effectiveness of colistin in the treatment of VAP and VAEs.

5. Conclusions

Based on the current evidence, colistin appears as effective and safe as β-lactam antibiotics for the treatment of MDR GNB VAP. AS colistin may be a beneficial adjunct to IV colistin in the management of MDR GNB VAP. Colistin combined therapy does not appear to provide better outcomes compared with colistin monotherapy. However, as these findings largely relied on data from observational studies, selection bias seems unavoidable, and therefore RCTs are needed to further confirm the role of colistin in the treatment of MDR GNB VAP.

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