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Review

Inhaled colistin monotherapy for respiratory tract infections in adults without cystic fibrosis: a systematic review and meta-analysis

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ABSTRACT

Background: Inhaled colistin is becoming increasingly popular against respiratory tract infections caused by multidrug resistant (MDR) Gram-negative bacteria because it may overcome the problems associated with intravenous (IV) administration.
Objective: To investigate the effectiveness and safety of inhaled colistin as monotherapy (without concomitant IV administration of colistin) in the treatment of respiratory tract infections caused by MDR or colistin–only susceptible Gram–negative bacteria.
Methods: PubMed and Scopus databases were searched. A systematic review and meta-analysis were conducted.
Results: Twelve studies (373 patients receiving inhaled colistin for respiratory tract infection) were included. Ten studies evaluated patients with pneumonia (including 8 studies with ventilator-associated pneumonia) and 2 studies evaluated patients with ventilator-associated tracheobronchitis. Patients with infections due to MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were mainly studied. Daily dose of inhaled colistin and treatment duration varied in the individual studies. The pooled all-cause mortality was 33.8% (95% CI 24.6% – 43.6%), clinical success was 70.4% (58.5% – 81.1%) and eradication of Gram-negative bacteria was shown in 71.3% (57.6% – 83.2%) of cases.
Conclusions: Inhaled colistin monotherapy may deserve further consideration as a mode for colistin administration for the treatment of respiratory tract infections caused by MDR *A. baumannii* and *P. aeruginosa*.
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1. Introduction

Respiratory tract infections caused by multidrug–resistant (MDR) and extensively drug–resistant (XDR) Gram-negative bacteria, particularly those of *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, have been associated with high morbidity and mortality, mainly among critically ill patients under mechanical ventilation [1–3]. The lack of effective antimicrobial therapy, mainly attributed to the emergence of resistance, was among the factors associated with mortality [4,5]. Colistin, a formerly 'abandoned' antibiotic, remains one of the few active antimicrobial agents against MDR and XDR Gram-negative bacteria [4], and is currently considered one of the last therapeutic options. However, the safety of intravenous (IV) colistin in critically ill patients has been debated because it has been associated with variable nephrotoxicity and neurotoxicity [6]. Moreover, the physicochemical characteristics of colistin predispose for low lung tissue penetration after IV administration, which may hamper its effectiveness in this group of patients [7,8].

The use of inhaled colistin is becoming increasingly popular because it may overcome the aforementioned problems associated with IV administration [9]. Several studies compared the effectiveness and safety of inhaled colistin in combination with IV colistin with that of IV colistin alone for the treatment of pneumonia, particularly ventilator-associated pneumonia (VAP) [10–13]. Recent systematic reviews showed that patient outcomes improved when inhaled colistin was added to the IV colistin–containing regimens [14,15]. In accordance, the latest guidelines by the Infectious Diseases Society of America and the American Thoracic Society suggested the adjunctive administration of inhaled colistin in patients with hospital–acquired pneumonia (HAP)/VAP caused by colistin-only susceptible pathogen in addition to IV polymyxin (colistin or polymyxin B) [16]. However, possible disadvantages of IV

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plus inhaled administration may include potential for higher nephrotoxicity, emergence of resistance, particularly in the respiratory tract, and elevated expenditures [16].

It has been suggested that inhaled colistin as monotherapy may result in lower systemic toxicity while achieving a higher drug concentration in the lung tissue early in the course of infection compared with IV colistin [17,18]. Thus, the aim of the present evaluation of published evidence was to investigate the effectiveness and safety of inhaled colistin as monotherapy (without concomitant IV administration of colistin) in the treatment of respiratory tract infections caused by MDR, XDR or colistin–only susceptible (COS) Gram-negative bacteria.

2. Methods

2.1. Literature search

Studies were identified by a systematic review of the literature in the PubMed and Scopus databases until October 2016 using the following search terms: (inhaled OR aerosolized OR nebulized) AND (colistin OR colistimethate sodium OR CMS) AND (pneumonia OR ventilator-associated pneumonia OR VAP OR tracheobronchitis OR VAT OR respiratory tract). The reference lists of selected articles and relevant reviews were searched for potentially eligible studies. Abstracts from international conferences were not searched.

2.2. Study selection and data extraction

Studies were considered eligible for inclusion, regardless of their design, if they investigated the effectiveness or safety of inhaled colistin monotherapy in the treatment of respiratory tract infections in adult patients without cystic fibrosis. Inhaled colistin could be used either as monotherapy (no other antibiotic was administered) or as adjunctive treatment to other IV antibiotics (active or inactive against the isolated pathogen) except for colistin. Patients receiving IV colistin in addition to inhaled colistin were excluded from the analysis. If IV colistin was administered in a minority (<20%) of patients included in a study, but separate data for these patients were not provided, the study was eligible for inclusion. Studies were excluded if they enrolled fewer than 10 patients. All relevant articles could be included, regardless of the language of publication. When studies included both infected and colonized patients, only the outcomes for the former were extracted. If additional data were required, the first or corresponding author of the study was contacted via e-mail.

2.3. Outcomes and definitions

The primary outcome measure was all-cause mortality in the inhaled colistin therapy group of patients regardless of the time point mortality was recorded. If all–cause mortality was not provided, infection–related mortality could be extracted. The secondary outcomes were clinical response, which was defined as clinical cure or improvement, and microbiological eradication. The definition of secondary outcomes was based on the definitions applied in the individual studies. MDR and XDR definitions were based on the definitions given in each study.

2.4. Data analysis

The meta-analysis was performed with MedCalc Statistical Software (Version 14.8, MedCalc Software, Ostend, Belgium). Pooled odds ratios (OR) or frequency and 95% confidence intervals (CI) were calculated using the random effect model, regardless of the observed heterogeneity as high across–study methodological and clinical heterogeneity was anticipated. Statistical heterogeneity among studies was assessed using a χ^2 test ($P < 0.10$ was defined to indicate significant heterogeneity) and I^2 (to assess the degree of heterogeneity for the whole analysis and for subgroup differences).

3. Results

3.1. Study selection and characteristics

Fig. 1 presents the study selection process (flowchart). Out of the initially identified articles, 12 studies (515 patients with respiratory tract infections, 373 patients receiving inhaled colistin monotherapy) were included: 2 randomized controlled trials (RCT), 2 case-control studies, and 8 cohort studies [17,19–29].

Table 1 shows the characteristics of the included studies. Ten studies examined patients with pneumonia; 5 ventilator-associated pneumonia (VAP) only [19,25,26,28,29], 2 nosocomial pneumonia (NP) and VAP [23,24] and 3 included patients with pneumonia without specifying the exact type [20–22]. Two studies enrolled patients with ventilator-associated tracheobronchitis (VAT) [17,27]. All studies provided definitions for the outcomes of the meta-analysis, but differences in these definitions were observed. In 6 studies, *A. baumannii* was the only pathogen studied [20–23,25,28]. In 6 studies, infections caused by *P. aeruginosa* were also included [17,19,24,26,27,29]. Two studies also included infections by Enterobacteriaceae and 1 study included infections by *Stenotrophomonas maltophilia* [17,19,27]. Six studies described the type of nebulizer (3 jet and 3 vibrating mesh nebulizers) [17,19,23,26,27,29]. The mean daily dose of inhaled colistin ranged between 1.25 to 15 MIU. The mean duration of colistin treatment varied from 7 to 17.5 days. All but two studies assessed patient severity of disease using APACHE II score (range between 7.0 and 23.1) on the first day of inhaled colistin.

Table 2 shows that in 5 studies, colistin was the only active agent against the causative pathogen of the respiratory infection; additional antibiotics inactive against the causative pathogens might have been administered in patients included in these studies. Additional antibiotics active against the causative pathogen were used in the

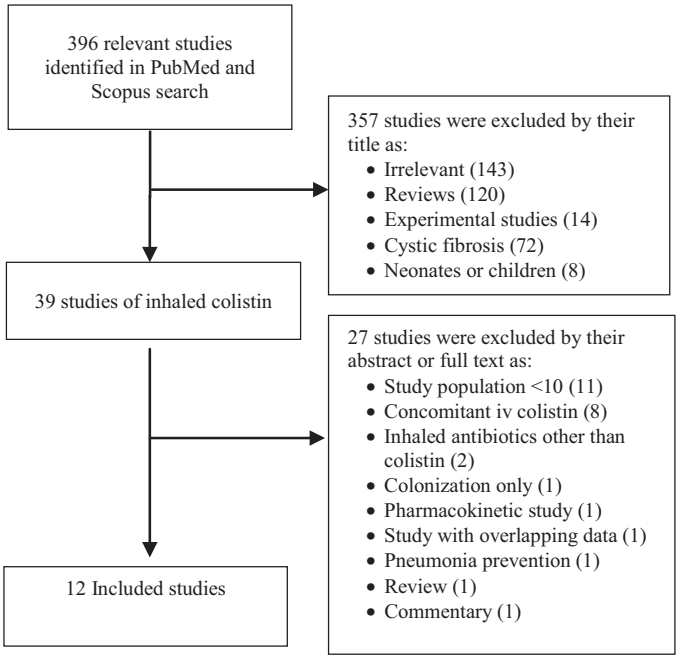

Fig. 1. Flow diagram of the study selection process.

Table 1
Study design and patient characteristics in the included studies

Study, year	Study design	Country	Type of infection (N of patients)	Number of patients (% males)		Age, years (mean ± SD)[g]		ICU N (%)		APACHE II score (mean ± SD)[g]		Daily inhaled colistin dosage[a], nebulizer type		Duration of inhaled colistin, days (mean ± SD)[g]
Two-arm studies				Inhaled colistin group	Control group	Inhaled colistin group	Control group	Inhaled colistin group	Control group	Inhaled colistin group	Control group	Inhaled colistin group	Control group	
Rattanaumpawan et al., 2010 [29]	Open label RCT	Thailand	VAP (53)	27 (63)	26 (69)	71.5 ± 15.9	63.3 ± 15.1	27 (100)	26 (100)	19.1 ± 5.8	18.5 ± 4.7	4.4 MIU, jet nebulizer	4 ml of NSS, jet nebulizer	9.5 ± 4.6
Kuo et al., 2012 [23]	Retrospective, matched case-control	Taiwan	NP (15) VAP (13)	16 (88)	12 (67)	76.4 ± 14.8	77.6 ± 11.1	9 (56)	11 (92)	21.8 ± 5.7	22.6 ± 5.5	4 MIU, jet nebulizer	None	11.1 ± 3.6
Chen et al., 2014[20] [b]	Retrospective cohort	Taiwan	Pneumonia (52)	24 (NR)	28 (NR)	74.9 ± 12	71.2 ± 15.7	NR	NR	19.8 ± 5.5	22.5 ± 5.4	4 MIU, NR	None	NR
Abdellatif et al. 2016 [19]	Single-blind RCT	Tunisia	VAP (149)	73 (70)	76 (64)	50 ± 16	53 ± 17	73 (100)	76 (100)	SOFA: 7.03 ± 3.8	SOFA: 6.5 ± 4.1	12 MIU, vibrating-mesh nebulizer	None [f]	≥14[d]
Single–arm studies														
Kwa et al., 2005 [24]	Retrospective cohort	Singapore	NP (18) VAP (3)	21 (57)		60.6 ± 15.0		17 (81)		23.1 ± 9.1		2.14 ± 0.47 MIU, NR		Median (range) 14 (2–36)
Motaouakkil et al., 2006 [28]	Observational cohort	Morocco	VAP (16)	16 (63)		44.3 ± 18.9		16 (100)		7.0 ± 3.3		3MIU, NR		15[e]
Lin et al., 2010 [25]	Retrospective cohort	Taiwan	VAP (45)	45 (71)		71 ± 15		45 (100)		18.9 ± 5.7		4.29 ± 0.82 MIU, NR		10.29
Athanassa et al., 2012 [17]	Prospective cohort	Greece	VAT (20)	20 (65)		64.9 ± 15.2		20 (100)		15.7 ± 6.7		3 MIU, vibrating-mesh nebulizer		7[c]
Lu et al. 2012 [26]	Prospective cohort	France	VAP (43)	43 (77)		Median: 58 (32–62)		43 (100)		SOFA, Median 9 (IQR 5–11)		15 MIU, vibrating-mesh nebulizer		12 (7–19)
Choi et al., 2014 [21]	Retrospective cohort	Korea	Pneumonia (11)	11 (64)		72 (±9.6)		10 (91)		19.7 ± 6.0		1.875 MIU, NR		17.5 ± 7.4
Maskin et al., 2015 [27]	Prospective cohort	Argentina	VAT (20)	20 (75)		Median: 67 (56–76)		20 (100)		Median: 23 (IQR 18–28)		1.25 MIU, jet nebulizer		7[c]
Hsieh et al., 2016 [22]	Retrospective cohort	Taiwan	Pneumonia (31) VAP (26)	57 (58)		79.4 ± 12.1		32 (56)		18.1 ± 6.5		4 MIU, NR		13.5 ± 6.5

[a] Some studies provided colistin dose in mg of colistin base activity (CBA); all dosages were converted to MIU (1 MIU CMS equals 80 mg CMS and approximately 34 mg CBA).
[b] Patient characteristics refer to all included patients (colonized and with pneumonia). Separate data for patients with pneumonia only were not provided.
[c] All patients in these 2 studies received treatment for 7 days.
[d] Inhaled colistin was administered for at least 14 days.
[e] All patients in this study received treatment for 15 days.
[f] IV colistin: loading dose 9 MIU, maintenance dose 9 MU.
[g] When indicated, the studies provided median (min-max) values.

Abbreviations: APACHE II: acute physiologic assessment and chronic health evaluation II, CBA: colistin base activity, CMS: colistimethate sodium, COS: colistin-only susceptible, ICU: intensive care unit, IQR inter-quartile range, MDR: multidrug resistant, NP: nosocomial pneumonia, NR: not reported, NSS: normal saline solution, RCT: randomized controlled trial, SD: standard deviation, SOFA: sequential organ failure assessment, VAP: ventilator-associated pneumonia, VAT: ventilator-associated tracheobronchitis, XDR: extended drug resistance.

Table 2
Characteristics of isolated Gram-negative bacteria and concomitant antibiotic use in the included studies

Study	Causative Pathogen, N of patients (%)			Susceptibility	Concomitant IV Antibiotics, N of patients (%)		
Two-arm studies							
		Inhaled colistin group	**Control group**			**Inhaled colistin group**	**Control group**
Rattanaumpawan et al [29]	CR *A. baumannii*	13 (48.1)	11 (42.4)	colistin[a]	carbapenems	15 (55.6)	15 (61.5)
	CR *P. aeruginosa*	2 (7.4)	2 (7.8)		TZP	4 (14.8)	9 (34.6)
					CFP/SUL	4 (14.8)	6 (23.1)
	Other GNB	14 (51.9)	14 (53.8)		3rd and 4th cephalosporins	4 (14.8)	4 (15.38)
Kuo et al [23]	MDR *A. Baumannii*	16 (100)	12 (100)	colistin [b] : 25/28 (89.3)	carbapenems	9 (56.2)	3 (25)
					SUL or SAM	5 (31.3)	3 (25)
					TGC	5 (31.3)	5 (41.6)
					anti-pseudomonal β-lactams	1 (6.3)	7 (58.3)
					CIP or LVX	2 (12.5)	3 (25)
Chen et al [20]**.**	MDR *A. Baumannii*	24 (100)	28 (100)	colistin [d]	TGC, SAM	NR	NR
Abdellatif et al [19]	*A. baumannii*	33 (45)	35 (46)	variable [c]	β-lactams	32 (44)	37 (49)
	P. aeruginosa	10 (14)	16 (21)		aminoglycosides	11 (15)	12 (16)
	Enterobacteriaceae	14 (19)	10 (13)		quinolones or macrolides	5 (7)	6 (8)
	S. maltophilia	2 (3)	3 (4)		tigecycline	8 (11)	8 (11)
	No isolated pathogen	14 (19)	12 (16)		glycopeptides	8 (11)	6 (8)
Single–arm studies							
Kwa et al [24]	MDR *A. baumannii*, 17 (81) MDR *P. aeruginosa*, 4 (19)			polymyxin only	carbapenems, TZP, AZT, SXT, VAN and/or CIP		
Motaouakkil et al [28]	MDR *A. baumannii*, 16 (100)			colistin only	RIF: 16 (100)		
Lin et al [25]	MDR *A. baumannii*, 25 (100)			colistin only	colistin: 6 (13), carbapenems: 39 (87)		
Athanassa et al [17]	POS *A. baumannii*, 11 (55) POS *P. aeruginosa*, 8 (40) POS *K. pneumoniae*, 2 (10)			polymyxin only	NR		
Lu et al [26]	MDR *A. baumannii*, 11 (26) MDR *P. aeruginosa*, 32 (74)			colistin, aminoglycosides and/or CIP	no IV antibiotic: 28 (65) 3-day aminoglycosides: 15 (34)		
Choi et al [21]	COS *A. baumannii*, 11 (100)			colistin only	TEC: 1 (9), VAN: 2 (18), CFP/SUL: 2 (18), LVX: 1 (9) MTZ: 1 (9), SXT: 1 (9), RIF: 1 (9)		
Maskin et al [27]	MDR *P. aeruginosa*, 17 (85) MDR *K. pneumoniae*, 3 (15)			only to colistin and aminoglycosides	no IV antibiotic		
Hsieh et al [22]	XDR *A. baumannii*, 57 (100)			colistin TGC: 28/57 (49.1)	no IV antibiotic: 9 (15), TGC: 29 (50.9), SUL: 6 (10.5), cephalosporins: 1 (1.8), carbapenems: 7 (12.3), colistin: 4 (7)		

[a] Isolates were resistant to anti-pseudomonal penicillins and cephalosporins, carbapenems, monobactams, quinolones, aminoglycosides, tetracyclines, and SXT.
[b] Isolates were resistant to IMP, CAZ, CFP, FEP, TZP, CIP, LVX, GEN, TET, SXT, SUL.
[c] Colistin only [inhaled colistin group: 13/73 (17.8%), control group: 12/76 (15.8%)].
[d] Isolates were carbapenem resistant, no data were reported for other drugs.

Abbreviations: ATM: aztreonam, CAZ: ceftazidime, CFP: cefoperazone, CIP: ciprofloxacin, COS: colistin-only susceptible, CR: carbapenems resistant, FEP: cefepime, GEN: gentamicin, GNB: Gram-negative bacteria, IPM: imipenem, LVX: levofloxacin, MDR: multidrug resistant, MTZ: metronidazole, NR: not reported, POS: polymyxin only susceptible, RIF: rifampicin, SAM: ampicillin-sulbactam, SUL: sulbactam, SXT: trimethoprim-sulfamethoxazole, TEC: teicoplanin, TET: tetracycline, TGC: tigecycline TZP: piperacillin-tazobactam, VAN: vancomycin.

remaining 7 studies; their precise percentage could not be specified. Table 3 presents the outcomes of the included studies.

3.2. Mortality

Mortality was reported in 8 studies (293 patients) with pneumonia. The pooled all–cause mortality was 33.8% (95% CI 24.6% – 43.6%, Fig. 2). Two controlled studies (one randomized and one matched case-control) were included in the comparative analysis (81 patients) of inhaled colistin versus no active inhaled treatment [23,29]. One study was excluded from this analysis as it enrolled a high percentage (70%) of colonized patients [20], and 1 RCT was excluded because patients in the control group received IV colistin [19]. There was no difference between the compared groups in terms of mortality (OR 1.11, 0.31 – 3.88; $I^2 = 68.2\%$). The lack of data according to specific doses or ranges of doses prevented a further subgroup analysis according to the inhaled colistin daily dosages (e.g., 'low' vs 'high' dosages).

3.3. Clinical success

Clinical success was reported in 10 studies (328 patients) with respiratory tract infections (including VAP, nosocomial pneumonia, pneumonia and VAT). The pooled clinical success was 70.4% (58.5% – 81.1%, Fig. 3). Excluding the two studies with VAT, the pooled clinical success was 65.9% (53.3% – 77.5%). Comparative data were not available.

3.4. Microbiological success

Microbiological success was assessed in 11 studies (292 patients). Eradication of Gram-negative bacteria with inhaled colistin was achieved in 71.3% (57.6% – 83.2%, Fig. 4). Similar eradication was reported among studies including only patients with pneumonia (71.5%, 57.3% – 83.9%, 9 studies) and respiratory infections due to *A. baumannii* only (71.1%, 53.8% – 85.7%, 6 studies). No difference was observed in microbiological eradication with inhaled colistin compared with no active inhaled treatment (OR 3.03, 0.31 – 29.7; $I^2 = 77.9$ %).

3.5. Safety

Most of the patients in the included studies tolerated inhaled colistin well. Eight studies provided specific data on nephrotoxicity using variable definitions (Table 3); the 4 remaining studies reported no significant differences from baseline serum creatinine or creatinine clearance values. Among patients receiving inhaled colistin, nephrotoxicity varied from 12% to 38%; 23 patients required renal replacement therapy. Two-arm studies showed no differences regarding nephrotoxicity between inhaled colistin and no active inhaled treatment groups. One study that compared inhaled with IV colistin showed significantly lower nephrotoxicity (13/73 [17.8%] vs. 30/76 [39.4%], $P = 0.004$) and need for renal replacement therapy (4/13 [30.7%] vs. 12/30 [40%], $P = 0.032$) in patients receiving inhaled colistin monotherapy. The two studies administering high daily dosage of inhaled colistin (12 MIU and 15 MIU) showed comparable nephrotoxicity (17.8% and 12%, respectively) to the studies evaluating low daily dose (4 MIU, 10–38%). Neurotoxicity frequency was low, but one discontinuation was reported. Bronchospasm was reported in seven cases; one patient discontinued inhaled colistin treatment.

4. Discussion

To the best of our knowledge, this is the first attempt to evaluate the literature regarding the use of inhaled colistin as monotherapy for the treatment of respiratory tract infections caused by Gram-negative bacteria, mainly MDR strains of *A. baumannii* and *P. aeruginosa*. Interestingly, only a few cases with *K. pneumoniae* infections were reported. When possible, patients treated with concomitant IV colistin and colonized patients were excluded from the analysis.

Although most of the included studies evaluated critically ill patients with VAP and high APACHE II score, mortality was comparable to that in studies of patients receiving IV colistin, primarily without inhaled colistin (23–55%) [10–13]. Inhaled colistin monotherapy also showed fair effectiveness, both microbiological and clinical. These were in accordance with the outcomes of studies comparing the use of IV colistin and IV plus inhaled colistin, in which the clinical and microbiological success was 18–75% [10–13]. Similar effectiveness between inhaled and IV colistin was also observed in the single RCT evaluating the comparative effectiveness of the two modalities [19]. Few data regarding adverse events were provided. Nephrotoxicity varied in the individual studies. Inhaled colistin showed significantly lower nephrotoxicity and need for renal replacement therapy compared with IV in the single available RCT [19].

Colistin physicochemical characteristics predispose for low lung tissue penetration after IV administration, as it is a very large, hydrophilic, cationic decapeptide [7,8]. Several studies evaluated colistin pharmacokinetics in the lungs of critically ill patients with respiratory tract infections following either IV or inhaled administration [17,18,30]. Variations in study population characteristics, timing of measurements and colistin doses, in combination with methodological difficulties in sampling and analysis, significantly affected the pharmacokinetic outcomes on colistin concentrations in lung compartments and fluids [7].

The first study indirectly assessing colistin concentrations in the epithelial lining fluid (ELF) after intravenous administration (CMS daily dose 6 MIU) showed that the achieved colistin concentration varies significantly, and sometimes may be insufficient as it resulted in undetectable colistin concentrations in bronchoalveolar lavage (BAL) 2 hours following colistin administration [30]. These findings were supported by similar, but variable, outcomes in animal studies even after a loading dose [8,31]. However, Boisson et al. showed that at steady state (2–4 days after initiation of IV infusion), IV colistin administration (2 MIU every 8 h) reached higher levels in ELF (at therapeutic concentrations, 1.28–28.9 mg/L) than in plasma [18]. It should be commented that a single 2 MIU dose of inhaled CMS was also administered in these patients on treatment initiation. Another study on 2 ICU patients that did not comment on the timing of colistin measurements reported similarly high colistin levels to that of Boisson et al [32]. These studies raised doubts regarding the adequacy of colistin levels in the lungs during the first hours following the initiation of IV treatment, and indicated that additional modalities may be required to achieve adequate colistin concentrations early during the course of infection [33].

When administered for the treatment of experimental lung infection models, inhaled colistin achieved higher concentrations in the BAL/lung tissue compared with IV administration [31,34]. In critically ill patients, a single 1 MIU dose of inhaled CMS achieved a median colistin concentration in ELF above 2 mg/L for the whole dosing interval (8 h) [17]. Boisson et al showed that after a 2 MIU dose of inhaled CMS, ELF colistin concentrations were even higher (9.53–1137 mg/L) and much higher than those in plasma, which indicates low systemic exposure and toxicity [18]. However, in both studies, colistin concentrations in ELF varied substantially among patients. In the present analysis, the daily doses of inhaled colistin used in most of the included studies were in the range of, or higher than, that used in the PK studies.

Studies have shown that delayed initiation of adequate antimicrobial treatment in critically ill patients with sepsis is associated

Table 3
Clinical, microbiological and mortality outcomes in the included studies

Study	Clinical success n/N (%)	Microbiological success n/N (%)	Mortality n/N (%)	Adverse events n/N (%)		
				Nephrotoxicity	Neurotoxicity	Bronchospasm
Two–arm studies*						
Rattanaumpawan et al [29]	10/27 (37) vs 12/26 (46.2)	17/27 (63) vs 16/26 (61.5)	15/27 (55.5) vs 11/26 (42.3)	8/27 (29.6) vs 3/26 (11.5)	none	1/27 (3.7) vs 1/26 (3.8)
Kuo et al [23]	NR	11/16 (68.8) vs 2/12 (16.7)	2/16 (12.5) vs 3/12 (25)	ARF: 2/16 (12.5) vs 3/12 (25), RRT: 1/16 (6.3) vs 2/12 (16.7)	NR	none
Chen et al [20]	NR	12/24 (50) vs NR	NR	AKI: 24/63 (38.1) vs 11/36 (30.6) [d]	NR	none
Abdellatif et al [19]	49/73 (67.1) vs 55/76 (72.4)	55/59 (93.2) vs 57/64 (89.1)	20/73 (27.4) vs 18/76 (23.7)	ARF: 13/73(17.8) vs 30/76 (39.4), RRT: 4/13 (30.7) vs 12/30 (40) [e]	9/73 (12) vs 7/76 (9.2)	2/73 (2.7) vs 0/76 (0)
Single-arm studies						
Kwa et al [24]	12/21 (57.1)	11/21 (52.4)	10/21 (47.6)	renal function did not differ significantly from baseline	none	1/21 (4.8) (discontinued)
Motaouakkil et al [24]	16/16 (100)	16/16 (100)	NR	renal function did not differ significantly from baseline	NR	NR
Lin et al [25]	26/40 (65) [a]	17/25 (68) [b]	19/45 (42.2)	none	none	none
Athanassa et al [17]	16/20 (80)	8/20 (40)	NR	no significant differences in CrCl	NR	NR
Lu et al [26]	29/43 (67.4)	NR	7/43 (16)	5/43 (12) renal function impairment	NR	NR
Choi et al [21]	9/11 (81.8)	5/11 (45.5)	4/11 (36.3)	AKI: 3/11 (27.3) (no discontinuation)	none	none
Maskin et al [27]	19/20 (95)	19/20 (95)	NR	2/20 (10) renal injury (increase S_{cr} > 50%)	1/20 (5) (treatment discontinued)	2/20 (10) (no discontinuation)
Hsieh et al [22]	29/57 (50.9)	42/53 (79.2) [c]	20/57 (35.1)	AKI: 12/57 (21) (no RRT)	none	2/118 [d] (1.7)

* Data reported as inhaled colistin group vs. control group.
[a] In 5 patients (11.1%), clinical success was classified as indeterminate (not possible).
[b] In 20 cases (44.4%), microbiological success was classified as indeterminate (not possible).
[c] Four out of 55 patients were excluded from the analysis as they received concomitant IV colistin.
[d] Data refer to both groups of patients (colonization and pneumonia) included in the study.
[e] Both ARF and RRT differences between inhaled colistin and IV colistin groups were statistically significant ($P = 0.004$ and $P = 0.032$, respectively).
Abbreviations: AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, CrCl: creatinine clearance, ID-related mortality: Infectious diseases-related mortality, NR: not reported, RRT: renal replacement therapy, S_{cr}: serum creatinine.

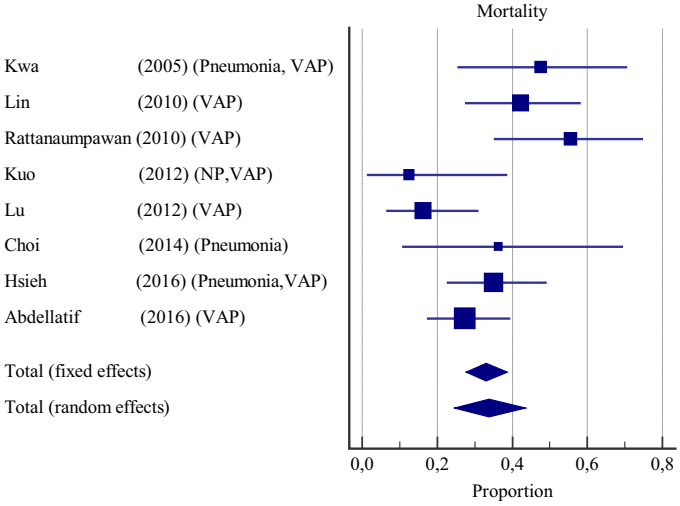

Fig. 2. Pooled analysis of mortality among patients treated with inhaled colistin. (Squares = proportion in each study; Horizontal lines = 95% CI; Diamonds = pooled proportion for all studies).

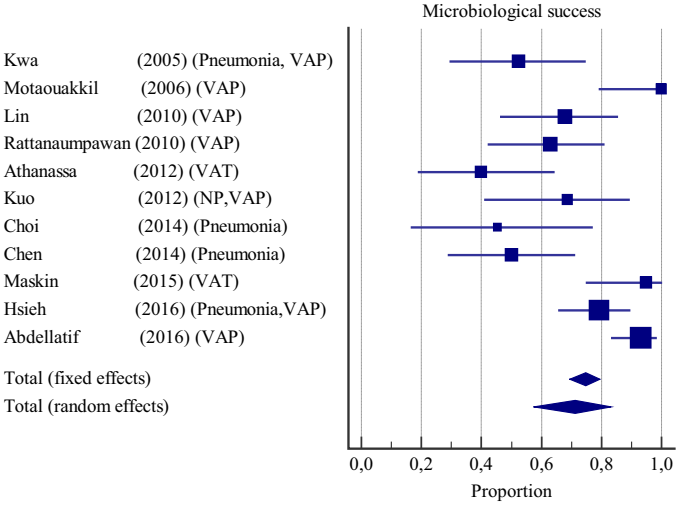

Fig. 4. Pooled analysis of microbiological success among patients treated with inhaled colistin. (Squares = proportion in each study; Horizontal lines = 95% CI; Diamonds = pooled proportion for all studies).

with increased mortality compared with patients without a delay in appropriate therapy initiation [35]. Particularly for those with VAP [36–38], inhaled colistin may have an advantage over IV administration as adequate colistin levels may be achieved earlier in lung compartments. Comparative data from well-designed RCTs are warranted to address this issue.

Critical parameters that may affect the effectiveness of inhaled colistin include the generator of the colistin aerosol, the delivery circuit and the patient's clinical status. Factors associated with the nebulizer are the production of aerosol droplet size, the extent of particle deposition and the residual volume [39]. Aerosol generators are divided into three main categories: jet, ultrasonic and vibrating-mesh nebulizers. Comparative data in studies showed that vibrating-mesh nebulizers are probably more efficient than the other two types. Mesh nebulizers combine higher and consistent aerosol drug delivery with negligible retention, and produce fine particles that can reach into the peripheral airways [40–45].

Patients with respiratory tract infections who are breathing spontaneously show critical differences in their ability to receive inhaled therapy compared with mechanically–ventilated patients. A variation of factors, including the patient's level of consciousness and inhalation techniques, may influence the extent of drug delivery to the lungs and consequently the success of the inhaled treatment [46]. The position of the patient, the breath pattern and the delivery circuit are the main differences between spontaneously breathing and mechanically–ventilated patients, probably affecting inhaled antibiotic effectiveness. Spontaneously breathing patients receive inhaled drugs by mouthpiece or facemask usually in a sitting position, keeping their own breathing pattern (rhythm and volume). In contrast, mechanically–ventilated patients are connected to a ventilator device via artificial airways (endotracheal tube and inspiratory limb), which configures the breathing parameters (air pressure, volume, and flow) [46,47].

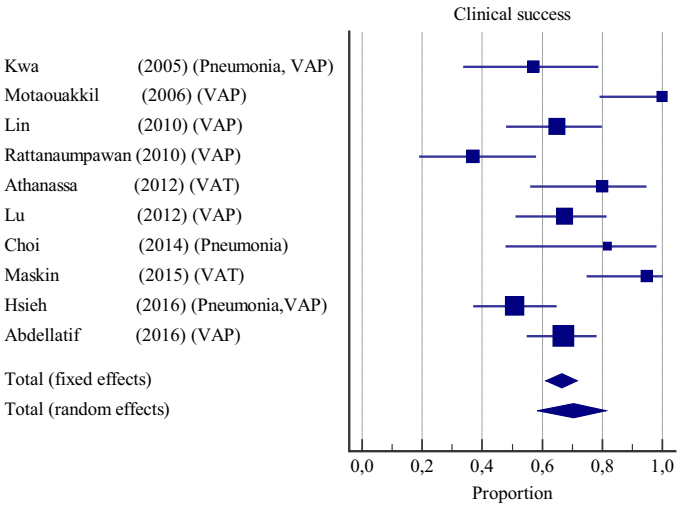

Fig. 3. Pooled analysis of clinical success among patients treated with inhaled colistin. (Squares = proportion in each study; Horizontal lines = 95% CI; Diamonds = pooled proportion for all studies).

Although some patients received additional, mainly inactive, IV antibiotics, the rationale behind the attending physicians' decision to treat patients with pneumonia (particularly VAP) with inhaled colistin only, instead of IV colistin or IV in combination with inhaled colistin, was not reported in most of the studies. One possible explanation could be the potential toxicity of IV colistin. As most of the studies included frail, elderly patients with high disease severity, physicians might have hesitated to prescribe IV colistin (high systemic exposure) in an effort to abate nephrotoxicity and neurotoxicity. In the single available RCT, IV colistin was associated with higher nephrotoxicity than inhaled [19]. Financial issues or insurance–related policies might have contributed in such treatment decisions. For example, in one of the studies the combination of colistin IV with inhaled was not compensated by the insurance systems [21]. Furthermore, the cost of the administration of IV and inhaled in combination is higher than either mode alone. Finally, another reason may be the administration of inhaled colistin as supportive treatment to patients with low expected long-term survival.

The findings of this systematic review are limited by the retrospective design of most of the studies, and the lack of control groups and adjustment for potential confounding factors. Thus, the effectiveness and safety of inhaled colistin monotherapy against MDR Gram–negative bacteria-induced lung infections compared with no treatment, IV colistin alone or IV plus inhaled colistin combination could not be evaluated. Furthermore, inhaled colistin dosing scheme (daily dose, dose intervals and treatment duration) was different between studies. In addition, a significant proportion of critically ill patients included in the analysis were under concurrent

systemic antibiotic therapy for remote sites of infections. This therapy was variable between studies and sometimes even unclear, so it was difficult to evaluate the effect of the co–administered antibiotics on the outcomes, even though in most of the cases colistin was the only active agent against the pneumonia-related pathogen. It has been reported that inactive antibiotics in vitro could be rendered active in the presence of other active or inactive antibiotics (synergy) [48–50]. Finally, the lack of data from sufficient studies did not allow further subgroup analysis according to the type of nebulizer, the inhaled colistin daily dosages (e.g., 'low' vs 'high' dosages), the duration of colistin treatment and the type of Gram-negative bacteria.

In conclusion, despite the aforementioned limitations, the clinical and microbiological outcomes of patients receiving inhaled colistin therapy as monotherapy seem to be encouraging. Thus, inhaled monotherapy may deserve further consideration as a mode for colistin administration for the treatment of respiratory tract infections due to MDR *P. aeruginosa* and *A. baumannii*. Well–designed, prospective and, if possible, randomized studies are required to evaluate further the effectiveness and safety of inhaled colistin monotherapy for the treatment of pulmonary infections, particularly VAP.

5. Declarations

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Competing interests: MEF participated in advisory boards of Achaogen, AstraZeneca, Infectopharm, Shionogi, Tetraphase, and Pfizer; received lecture honoraria from Cipla, Merck, Sanofi and Novartis; and received research support from Angelini, Astellas, Rokitan, and Shionogi. The rest of the authors have nothing to declare.

Ethical approval: None.

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