International Journal of Antimicrobial Agents xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Review

Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 13 August 2015
Accepted 28 September 2015

Keywords:
Aerosolised colistin
Adjuvant therapy
Nosocomial pneumonia
Multidrug-resistant Gram-negative bacteria
Meta-analysis

ABSTRACT

Colistin has been used to treat nosocomial pneumonia (NP) caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) via different administration routes. Whether patients may benefit from aerosolised colistin as adjunctive treatment was contradictory. We aimed to clarify the safety and efficacy of administering aerosolised and intravenous (IV-AS) colistin versus intravenous (IV) colistin alone in patients with NP caused by MDR-GNB. Two reviewers independently evaluated and extracted data from PubMed, EMBASE and Cochrane databases. Primary outcomes were clinical response rate, all-cause mortality (ICU or hospital), microbiological eradication and nephrotoxicity. Pooled odds ratios (ORs) were calculated and significance was determined by the *Z* test. Nine eligible studies involving 672 participants were included. The overall clinical response rate (improvement and cure) was significantly higher in the IV-AS group than that in the IV group [OR = 1.81, 95% confidence interval (CI) 1.30–2.53; *P* = 0.0005]. Patients treated with IV-AS colistin showed a higher rate of pathogen eradication (OR = 1.66, 95% CI 1.11–2.49; *P* = 0.01) and lower all-cause mortality compared with IV colistin (OR = 0.69, 95% CI 0.50–0.95; *P* = 0.02). Nephrotoxicity did not differ significantly between IV-AS and IV groups (five studies; 383 patients) (OR = 1.11, 95% CI 0.69–1.80; *P* = 0.67). These data indicate that IV-AS colistin has additional benefits compared with IV colistin alone. Clinicians should be encouraged to give combined administration routes in critically ill patients with NP caused by MDR-GNB.

1. Introduction

The prevalence of multidrug-resistant (MDR) Gram-negative bacteria (GNB) is relatively high in the intensive care units (ICU) setting [1]. Ventilator-associated pneumonia (VAP) or hospital-acquired pneumonia due to MDR pathogens (*Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) are leading healthcare-associated infections in ICU patients [2–4].

A lack of efficient antibiotics against MDR-GNB led to the re-introduction of polymyxin, which was abandoned in the 1980s due to serious adverse events [2,5]. Colistin, also known as polymyxin E, is a cyclic amphipathic antibiotic with excellent bactericidal activity against Gram-negative aerobic bacilli [6]. Its cationic characteristic makes it prone to bind to the lipopolysaccharide of the bacterial cell membrane of GNB, leading to leakage of intracellular contents and cell death. Colistin shows microbiological activity against MDR-GNB and serves as almost the last resort for extremely drug-resistant pathogens, but the serious adverse effects associated with the intravenous route drove clinician to try an inhaled or aerosolised formulation. Inhaled colistin has been administered for the successful eradication of pathogens from the respiratory tract in cystic fibrosis patients [7–11]. The clinical response rates of polymyxin E (colistin, colistimethate sodium) varied from 25% to 83.3% in treating VAP caused by MDR-GNB via different administration routes [12,13]. Aerosolised (AS) colistin as adjunctive treatment was reported to be beneficial in the management of VAP [13,14]. Meanwhile, other similar studies showed that addition of AS colistin to intravenous (IV) colistin did not provide any additional therapeutic benefit for patients with VAP due to MDR-GNB

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http://dx.doi.org/10.1016/j.ijantimicag.2015.09.011
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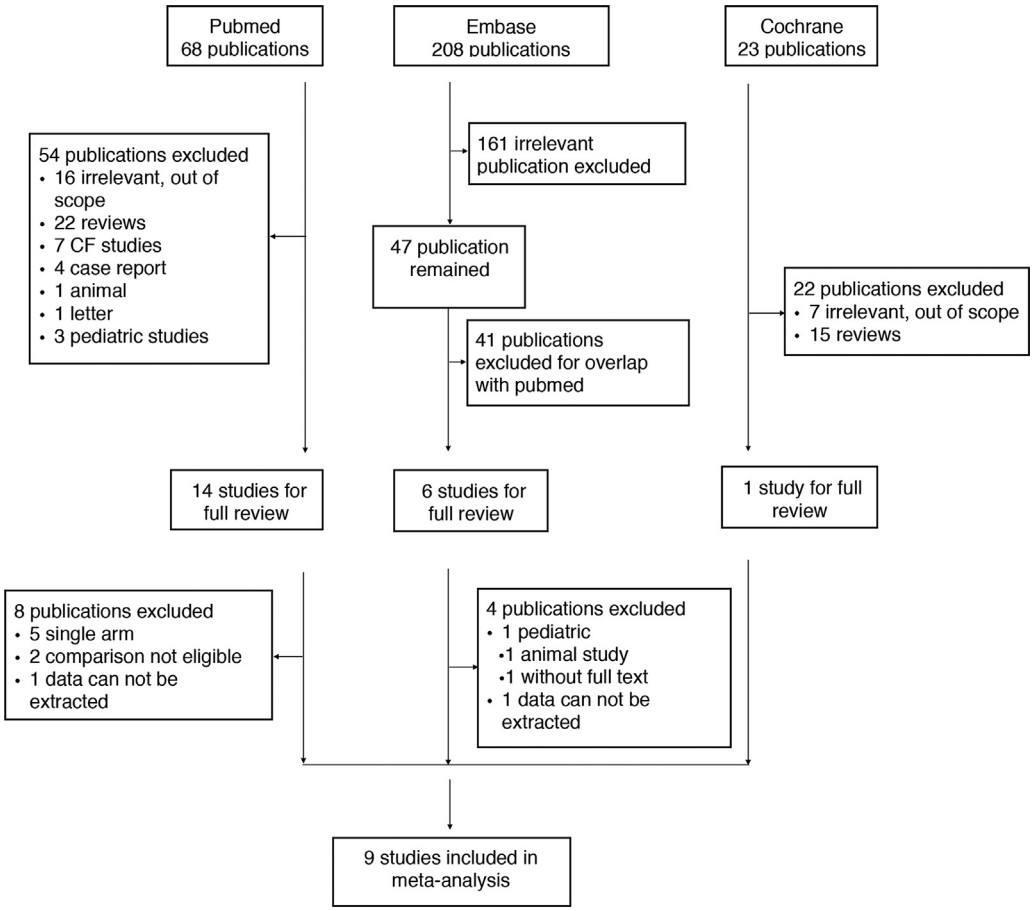

Fig. 1. Flow chart of study selection. CF, cystic fibrosis.

[15], and AS colistin combined with IV colistin was not superior to IV colistin alone in improving overall and VAP-related mortality [13–15]. In another study, AS colistin had no additional effect on the outcomes of patients; however, the nephrotoxicity rate was higher (41% vs. 19%) in patients who received AS colistin therapy [16].

These incompatible findings prompted the necessity to perform a systematic evaluation of the published evidence regarding the efficacy and safety of administering aerosolised and intravenous (IV-AS) colistin versus intravenous (IV) colistin alone in patients with nosocomial pneumonia (NP) caused by MDR-GNB.

2. Methods

2.1. Literature search

A literature search was performed using PubMed search engines via the library of Fudan University (Shanghai, China) from their inception until 21 November 2014. The Cochrane Central database and EMBASE were also searched for relevant studies published from their inception until 21 November 2014. No language restriction was imposed. The search strategies were as follows: ('colistin' [MeSH Terms] OR polymyxin E OR colistimethate sodium OR colistin methanesulfonate OR CMS) AND ('inhalation' [MeSH Terms] OR inhaled OR nebulised OR aerosolised) AND ('injection' [MeSH Terms] OR intravenous OR parenteral OR I.V) AND ('Humans' [Mesh Terms]).

2.2. Study selection

Two authors (DL and H-XL) independently reviewed the abstracts of all of the studies generated by the literature search. Studies were considered eligible and were included in the meta-analysis if they reported a comparison of the efficiency and safety of colistin by different administration routes. Studies reporting treatment outcome and adverse effects with two arms (IV-AS versus IV) were included. Single-arm studies with only one colistin administration route were excluded. No language restrictions were applied. Fig. 1 shows the search method.

2.3. Data extraction

The following extracted information was recorded: name of authors; publication year; type of study design; country where the study was performed; sex and age of patients; sample size; infectious disease; severity of illness [Acute Physiology and Chronic Health Evaluation (APACHE) II score]; type and dose of colistin administered; co-administration of other antibiotics; length of therapy; type of micro-organism; antibiotic susceptibility testing performed; clinical response rate (improvement and cure); microbiological eradication; length of ICU and hospital stay; all-cause mortality; and nephrotoxicity.

2.4. Definitions

2.4.1. Nosocomial pneumonia

NP was defined as pneumonia that occurred ≥48 h after hospital admission. Pneumonia was diagnosed by finding of a new

Please cite this article in press as: Liu D, et al. Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and meta-analysis. Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2015.09.011