

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

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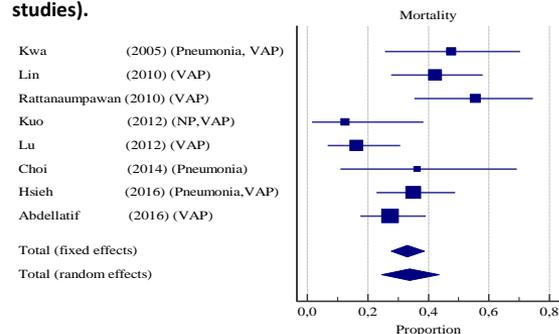
**Background:** Inhaled colistin is becoming increasingly popular against respiratory tract infections due to multidrug resistant (MDR) Gram-negative bacteria since it may overcome the problems associated with IV administration. We evaluated the effectiveness and safety of inhaled colistin as monotherapy (without concomitant intravenous administration of colistin) in the treatment of patients without cystic fibrosis and respiratory tract infections due to MDR or colistin only susceptible Gram-negative bacteria.

**Material/methods:** Studies were identified by a systematic review of the literature in the PubMed and Scopus databases until October 2016 using the 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).

Inhaled colistin could be used either only as monotherapy (no other antibiotic was administered) or as adjunctive treatment to other intravenous (IV) antibiotics (active or inactive to the isolated pathogen) except for colistin. Patients receiving IV colistin in addition to inhaled colistin were excluded from the analysis.

A one-way meta-analysis of observational data was conducted with MedCalc Statistical Software (Version 14.8, MedCalc Software, Ostend, Belgium).

**Figure 1. 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).**



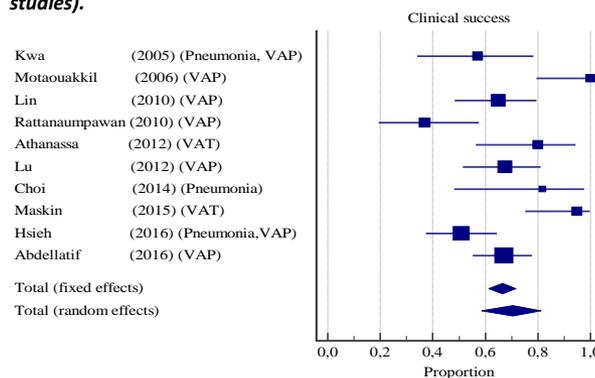
**Results:** Twelve studies (373 patients receiving inhaled colistin for respiratory tract infection) were included. Two randomized trials were identified. Ten studies evaluated patients with pneumonia (8 with VAP) and 2 with VAT. Patients with infections due to MDR *A. baumannii* and *P. aeruginosa* were mainly studied, but infections by Enterobacteriaceae and *S. maltophilia* were also identified.

Daily dose of inhaled colistin (1.25-15 million IU) and treatment duration (mean 7 to 17.5 days) varied in the individual studies.

In 5 studies colistin was the only active agent against the causative pathogen of the respiratory infection; additional inactive antibiotics against the causative pathogens might have been administered. Additional antibiotics active against the causative pathogen were used in the remaining 7 studies. Mortality was reported in 8 studies (293 patients) with pneumonia. The pooled all-cause mortality was 33.8% (95% CI 24.6% – 43.6%, figure 1).

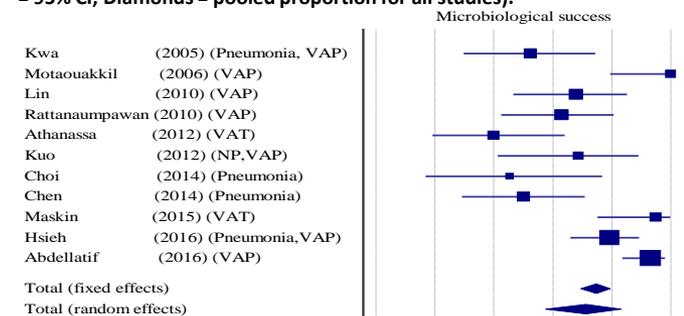
Clinical success was reported in 10 studies (328 patients with respiratory tract infections including VAP, and VAT). Clinical success was 70.4% (58.5% – 81.1%, figure 2); excluding the two studies with VAT, the pooled clinical success was 65.9% (53.3% – 77.5%). Eradication of Gram-negative bacteria was shown in 71.3% (57.6% – 83.2%) of cases.

**Figure 2. 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).**



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%, Figure 3). 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).

**Figure 3. 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).**



**Conclusions:** Despite that most of the included studies evaluated critically ill patients with VAP and high APACHE II score, mortality, microbiological and clinical effectiveness were comparable to that in studies of patients receiving IV colistin, primarily without inhaled colistin [1,2].

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.

Inhaled colistin monotherapy may deserve further consideration as a mode for colistin administration for the treatment of patients with respiratory tract infections due to MDR *A. baumannii* and *P. aeruginosa*.

## References:

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- Falagas ME, Rafailidis PI, Ioannidou E, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. Int J Antimicrob Agents. 2010;35(2):194-9