Clinical efficacy and safety of colistin treatment in patients with pulmonary infection caused by *Pseudomonas aeruginosa* or *Acinetobacter baumannii*: a meta-analysis

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Abstract

Introduction: The aim of this study was to evaluate the efficacy and safety of colistin treatment in patients with pulmonary infection caused by *Pseudomonas aeruginosa* or *Acinetobacter baumannii*.

Material and methods: The relevant studies were identified through a search of public databases including PubMed, MEDLINE and EMBASE up to December 2012. A meta-analysis was conducted to compare the clinical response, mortality and renal damage of colistin (colistin group) versus other effective antibiotics (control group). The odds ratio (OR) was chosen as the effect size.

Results: A total of 9 studies were eventually identified. The result of the meta-analysis showed that the pooled OR of clinical response was 1.24 (95% CI = 0.68–2.27, p > 0.05) for patients in the colistin group versus the control group, indicating no significant difference in efficacy between colistin and control groups. Similar results were obtained by the further subgroup meta-analyses by sample size, research year, ethnicity and study method. Treatment with colistin versus other agents did not affect hospital mortality (OR = 1.05, 95% CI = 0.58–1.89, p > 0.05) or renal damage (OR = 1.25, 95% CI = 0.78–2.00, p > 0.05). The combined estimate of our analysis was strong across multiple sensitivity analyses and without significant publication bias.

Conclusions: Our results suggest that colistin may be as efficacious and safe as standard antibiotics for the treatment of pulmonary infection.

Key words: colistin, pulmonary infection, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, meta-analysis.

Introduction

Multidrug-resistant (MDR) gram-negative bacilli, mainly *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Acinetobacter baumannii* (*A. baumannii*), are major nosocomial pathogens worldwide [1–3]. The emergence of infections caused by multidrug-resistant Gram-negative bacteria poses a great challenge for infection control [4–6].

Colistin, also called polymyxin E, is a polypeptide antibiotic. Colistin is commercially available as colistin sulfate (for oral and topical use) and colistimethate sodium (for parenteral use, intravenously and intramuscularly) [7]. Also, both forms can be administered by inhalation [8].
Clinical efficacy and safety of colistin treatment in patients with pulmonary infection caused by *Pseudomonas aeruginosa* or *Acinetobacter baumannii*: a meta-analysis

Although colistin showed excellent activities against many species of gram-negative bacteria *in vitro* [9, 10], use of colistin has been limited due to limited clinical efficacy and significant nephrotoxicity and neurotoxicity. During the last 2 decades, colistin was mainly restricted to treat acute exacerbations of lung infections in patients with cystic fibrosis [5, 11, 12]. However, the increasing frequency of pulmonary infections and lack of new agents effective against the resistant strains have led to the reconsideration of colistin [8]. Some reports have demonstrated that modified dosage of colistin could be used as a therapeutic intervention for patients with pulmonary infections due to MDR *P. aeruginosa* and *A. baumannii* [7, 8, 13, 14].

Nevertheless, whether colistin in the treatment of Gram-negative bacteria infection is superior to other antibiotics is controversial [15–18]. Meta-analysis is a statistical procedure for combining the results of several studies to produce a single estimate of the major effect with enhanced precision [19–21], and it is considered as a powerful tool for summarizing inconsistent results from different studies. Hence, the aim of the present meta-analysis was to systematically evaluate the efficacy and safety of colistin in the treatment of pulmonary infection caused by *P. aeruginosa* or *A. baumannii*.

Materials and methods

Literature search

Electronic databases including PubMed, MEDLINE, EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google Scholar were searched for all publications on colistin treatment in patients with pulmonary infection caused by *P. aeruginosa* or *A. baumannii* up to December 2012 without language restrictions. The main search terms were “colistin” OR “polymyxin” OR “polymyxin E” AND “pulmonary infection” OR “lung infection” AND “Pseudomonas aeruginosa” OR “Acinetobacter baumannii” OR “Gram-negative bacilli” AND “study” OR “trial”. Meanwhile, references from retrieved papers were checked for any additional studies. We only recruited data from the full published paper, not any meeting or conference abstract. Two investigators (HZ and QZ) independently searched the electronic databases.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: 1) The investigations concerned patients with bronchiectasis (prospective studies, retrospective studies or cross-sectional studies, etc.); 2) The objects were the pulmonary infected patients (range of age was not limited); 3) The method of treatment was colistin against other relevant antibiotic treatment (ways of application of the drugs were not limited); 4) The effect size was the odds ratio. Sample size was not limited; 5) Studies were published in the English language. Studies were excluded if one of the following existed: 1) reduplicated studies or records; 2) review of literature; 3) no control design.

Quality assessment and data extraction

Quality was assessed using the factors mainly including the methods of studies, sample size, and recruitment of respondents. Initial screening was done by reading the document title and abstract. Secondary screening was conducted by reading the full text of papers. Finally, studies were included according to the inclusion and exclusion criteria. Data items included study details (such as the first author’s name, research year of study, year of publication, location of participants, and method of studies), characteristics of participants (such as age and sample size), and Acute Physiological and Chronic Health Evaluation II (APACHE II) score. We contacted authors of the included studies to obtain further information about data items. We used standardized data extraction forms to record the first author’s name, time of study, time of publication, country, geographic location, sample size, age, study method and events of the colistin group versus the control group. Quality assessment and data extraction were independently conducted by two investigators. Disagreements were resolved by discussion to come to an agreement.

Statistical analysis

Our primary analysis was focused on a comparison of the odds ratios (ORs) in the colistin treated versus non-colistin treated patients with pulmonary infection caused by *P. aeruginosa* or *A. baumannii* (colistin group vs. control group). Then, stratified analysis by sample size, research year, participants’ geographic location and study method was also conducted.

The meta-analysis was performed using fixed or random effect models. The point estimates of the odds ratio (OR) and its 95% confidence interval (95% CI) were estimated for each study. We assessed the within- and between-study variation or heterogeneity by testing Cochran’s Q-statistic and *I*-statistic [22, 23]. Values of *p* < 0.10 or *T*-value > 50% was considered to be heterogeneous. When heterogeneity was detected across studies, the random effect model was used for meta-analysis as well as to take into account the possibility of heterogeneity between studies. Otherwise, the fixed effect model was used. The fixed effect model assumes that all of the studies are estimating the same underlying effect and considers...
Meta-analysis of efficacy of colistin versus other antibiotics

Overall meta-analysis as well as subgroup meta-analyses by sample size, research year, participants’ geographic location (ethnicity) and study method were conducted to compare the efficacy of colistin against other antibiotics in treatment of pulmonary infection caused by *P. aeruginosa* or *A. baumannii*.

As shown in Table II and Figure 2, a total of 9 separate studies [1, 9, 16, 27–32], consisting of 940 patients (411 in the colistin group and 529 in the control group) were included in this meta-analysis. There was significant heterogeneity across the studies ($Q^2 = 29.9$, $I^2 = 73.2\%$, $p < 0.01$). The overall meta-analysis indicated that the pooled OR was 1.24 (95% CI = 0.68–2.27, $p > 0.05$) for patients in the colistin group versus patients in the control group. The funnel plot was not symmetrical obviously, indicating that publication bias may exist. However, the result of Egger’s linear regression showed no publication bias in the studies included in this meta-analysis ($t = 1.76$, $p > 0.05$).

The results of the further subgroup meta-analyses are shown in Table II. The pooled OR was 0.75 (95% CI = 0.41–1.38, $p > 0.05$) when considering 4 studies in which the sample size was more than or equal to 40, and the pooled OR was 2.15 (95% CI = 0.92–5.00, $p > 0.05$) when considering 5 studies in which the sample size was less than...
### Table I. Characteristics of studies included in the meta-analysis

| Study                | Publication year | Research year | Country    | Ethnicity | Study method          | Group                              | Sample size | Age (mean ± SD or min-max) [years] | Drug and dose                                | APACHE II score (mean ± SD) |
|----------------------|------------------|---------------|------------|-----------|-----------------------|------------------------------------|-------------|------------------------------------|----------------------------------|-----------------------------|
| Betrosian et al.     | 2008             | NA            | Greece     | European  | Cohort study          | Colistin group 15                  | 67 ±9       |                                    | Colistin (3 MU every 8 h)       | 14 ±2                       |
|                      |                  |               |            |           |                       | Control group 13                  | 72 ±5       |                                    | Ampicillin/sulbactam (9 g every 8 h) | 14 ±5                       |
| Durakovic et al.     | 2011             | 2002–2006     | Croatia    | European  | Case-control study    | Colistin group 26                  | 35 (17–60)  |                                    | Colistin (3 MU every 8 h)       | NA                          |
|                      |                  |               |            |           |                       | Control group 26                  | 37 (18–63)  |                                    | Cefepime, meropenem, or piperacillin/tazobactam | NA                          |
| Garnacho-Montero et al. | 2003           | 1997–2001     | Spain      | European  | Cohort study          | Colistin group 21                  | 56.9 ±13.1  |                                    | Colistin (2.0–5.0 mg/kg per day) | 19.6 ±7.2                   |
|                      |                  |               |            |           |                       | Control group 14                  | 64.5 ±11.0  |                                    | Imipenem-clastatin (2–3 g per day) | 20.5 ±7.0                   |
| Hachem et al.        | 2007             | 2001–2004     | United States | America  | Case-control study    | Colistin group 31                  | 52 (10–72)  |                                    | Colistin (5.0 mg/kg per day)    | 17 (11–27)                  |
|                      |                  |               |            |           |                       | Control group 64                  | 62 (3–82)   |                                    | A β-lactam antibiotic or a quinolone | 16 (7–32)                   |
| Kallel et al.        | 2007             | 2003–2005     | Tunisia    | Africa    | Case-control study    | Colistin group 60                  | 43.4 ±18.8   |                                    | Colistin (6 MU per day)         | NA                          |
|                      |                  |               |            |           |                       | Control group 60                  | 41.4 ±16.7   |                                    | Imipenem (2 g per day)         | NA                          |
| Koomanachai et al.   | 2007             | 2005–2006     | Thailand   | Asian     | Cohort study          | Colistin group 78                  | 63.5 (18–103) |                                    | Colistin (5.0 mg/kg per day)    | 21.9                        |
|                      |                  |               |            |           |                       | Control group 15                  | 58.9 (27–90) |                                    | Other antibiotics              | 22.3                        |
| Oliveira et al.      | 2008             | 1996–2004     | Brazil     | America   | Case-control study    | Colistin group 82                  | 63 (8–87)    |                                    | Colistin (5.1 MU per day)       | 15 (3–39)                   |
|                      |                  |               |            |           |                       | Control group 85                  | 54 (7–89)    |                                    | Ampicillin/sulbactam (9 g per day) | 16 (1–50)                   |
| Reina et al.         | 2005             | 2000–2004     | Argentina  | America   | Cohort study          | Colistin group 55                  | 40 ±16       |                                    | Colistin (5.0 mg/kg per day)    | 21 ±7                        |
|                      |                  |               |            |           |                       | Control group 130                 | 41 ±16       |                                    | Carbapenems, sulbactam, tazobactam, etc. | 20 ±7                        |
| Qin et al.           | 2012             | 2006–2010     | France     | European  | Cohort study          | Colistin group 43                  | 58           |                                    | Colistin (5 MU every 8 h)       | NA                          |
|                      |                  |               |            |           |                       | Control group 122                 | 59           |                                    | Relevant intravenous antibiotics | NA                          |

NA – not available, MU – million units.
The pooled OR was 3.28 (95% CI = 0.31–34.37, p > 0.05) for studies published in or after 2005, and the pooled OR was 0.83 (95% CI = 0.36–1.91, p > 0.05) for studies published before 2005. The pooled OR was 1.13 (95% CI = 0.65–1.94, p > 0.05) for studies conducted in Europe and 0.80 (95% CI = 0.29–2.22, p > 0.05) for studies conducted in America. The pooled ORs were 1.49 (95% CI = 0.63–3.54, p > 0.05) and 1.03 (95% CI = 0.40–2.63, p > 0.05) for 5 cohort studies and 4 case-control studies, respectively.

No significant difference in efficacy between the colistin group and the control group was detected using overall and subgroup meta-analyses (p > 0.05).

Meta-analysis of mortality of colistin versus other antibiotics

As shown in Figure 3, a total of 7 separate studies [1, 9, 16, 27, 29, 31, 32], consisting of 635 patients (296 in the colistin group and 339 in the control group) with pulmonary infection caused by *P. aeruginosa* or *A. baumannii* were included in this meta-analysis. Significant heterogeneity was detected between studies ($Q^2 = 12.0, I^2 = 50.0\%$, p < 0.1). The overall meta-analysis indicated that the pooled OR was 1.05 (95% CI = 0.58–1.89, p > 0.05) for patients in the colistin group versus patients in the control group. No significant difference in mortality was observed between the colistin group and the control group. No publication bias was detected in the studies included in this meta-analysis using Egger's linear regression test. The result showed that there was no publication bias in the studies included in this meta-analysis ($t = 1.54, p > 0.05$).

Meta-analysis of renal damage of colistin versus other antibiotics

As shown in Figure 4, a total of 6 separate studies [1, 9, 16, 27, 29, 32], consisting of 470 patients (253 in the colistin group and 217 in the control group) with pulmonary infection caused by *P. aeruginosa* or *A. baumannii* were included in this meta-analysis. No heterogeneity between studies was detected ($Q^2 = 8.22, I^2 = 39.0\%$, p > 0.1). The overall meta-analysis indicated that the pooled OR was 1.25 (95% CI = 0.78–2.00, p > 0.05) for patients in the colistin group versus patients in the control group. There was no significant difference in renal damage between the colistin group and the control group. No publication bias was detected in the studies included in this meta-analysis using Egger's linear regression ($t = 1.49, p > 0.05$).

Evaluation of sensitivity analysis

We performed a sensitivity analysis by removing one study each time and rerunning the mod-
el for the remainder of the studies to determine the effect on each overall estimate. The results showed that none of the individual studies substantially influenced the pooled ORs, which implied that our results were statistically reliable.

**Discussion**

In the present meta-analyses, we retrieved 9 studies focused on the efficacy and safety of colistin treatment in the patients with pulmonary infection caused by *P. aeruginosa* or *A. baumannii*. We found that no significant difference in efficacy, mortality and renal damage was detected between colistin and other effective antibiotics. The combined estimate of our analysis was strong across multiple sensitivity analyses and without significant publication bias.

Due to its unsatisfactory efficacy and significant nephrotoxicity and neurotoxicity, use of colistin was limited in clinical practice [13, 33]. How-
ever, colistin recently re-entered clinical use with the increasing emergence of MDR Gram-negative bacteria in hospitals [7, 8, 15]. Thus, it is necessary to reassess the efficacy and safety of colistin treatment. However, the results were inconsistent among previous studies due to small sample sizes or low statistical power. For example, Oliveira et al. reported that ampicillin/sublactam appears to be a more efficacious therapy than colistin, while Betrosian et al. suggested that colistin and ampicillin/sublactam were comparably safe and effective treatments. We combined 9 studies and found that compared to other effective agents, colistin showed no significant difference in efficacy when treating pulmonary infection caused by MDR P. aeruginosa or A. baumannii.

The degree of heterogeneity is one of the major concerns in meta-analysis for the validity of the meta-analysis [34, 35], as non-homogeneous data are liable to result in misleading results. Significant heterogeneity was detected when comparing the efficacy of colistin treatment. To investigate whether the sample size, research year, participants’ geographic location (ethnicity) or study method influenced the result, we also conducted a subgroup meta-analysis. We found that the heterogeneity between studies was decreased after stratifying the samples according to their different subgroups. For American samples, significant heterogeneity was observed under the recessive model, while no statistically significant heterogeneity was observed under any model in European samples. The results indicated that ethnicity might play an important role in genetic heterogeneity of patients with pulmonary infection caused by P. aeruginosa or A. baumannii. The subgroup analysis of clinical response also showed that there was no significant difference between colistin and control groups, suggesting that colistin and other antibiotic therapies are equally efficacious. Asia and Africa as participants’ geographic location were not included in the subgroup analyses, due to there being only one study in each region. In addition, dosage and ways of application of drugs were not investigated using the subgroup meta-analysis because these data cannot be extracted in all literatures.

Safety of colistin treatment was also compared with that of other antibiotic therapies using overall meta-analysis. We found that neither hospital mortality nor renal damage was affected by the treatment with colistin or other effective agents, suggesting that colistin also acts as a safe drug in the treatment of pulmonary infection. Actually, colistin is a concentration-dependent drug [36, 37]. In clinical practice, the dosage of colistin was adjusted according to the level of serum creatinine that represents renal function [32]. Thus, no significant renal toxicity of colistin could be explained.

Publication bias is another important factor affecting the quality of meta-analysis. Meta-analyses are prone to publication bias, the problem of selective publication of studies with positive results [38]. The result of Egger’s test demonstrated that there was no publication bias in this study (all p values > 0.05). Moreover, the result of sensitivity analysis by removing one study each time and re-running the model to determine the effect on each overall estimate implied that our results were statistically reliable.

Some limitations of this study should be discussed. First of all, only published studies were included in the present meta-analysis. Thus, publication bias may have occurred, although the use of a statistical test did not show it. Secondly, significant between-study heterogeneity was detected in the current meta-analysis, and may be distorting the meta-analysis. However, it was not a major problem because we did subgroup analysis to reduce the heterogeneity. Meanwhile, different populations may contribute to the heterogeneity. These results should be interpreted with caution because the population from each country was not uniform. Finally, considering that recruitment studies were non-RCT and the number of studies was small, more high-quality RCTs are needed to test and verify the results of this meta-analysis. Therefore, we minimized the likelihood of bias by developing a detailed protocol before initiating the study, performing a meticulous search for published studies and using explicit methods for study selection, data extraction and data analysis.

In conclusion, our findings suggest that colistin is a safe and effective drug and could be used as an alternative agent in patients with pulmonary infection caused by MDR P. aeruginosa or A. baumannii.

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Conflict of interest
The authors declare no conflict of interest.

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