What Is the Efficacy and Safety of Colistin for the Treatment of Ventilator-Associated Pneumonia? A Systematic Review and Meta-Regression

Diana F. Florescu,¹ Fang Qiu,² Megan A. McCartan,³ Cezarina Mindru,¹ Paul D. Fey,⁴ and A. C. Kalil¹

¹Infectious Diseases Division, ²Biostatistics Department, ³Department of Pharmaceutical and Nutrition Care, and ⁴Pathology Microbiology Department, Nebraska Medical Center, Omaha

Background. Experience with intravenous and aerosolized forms of colistin for the treatment of ventilator-associated pneumonia (VAP) in patients without cystic fibrosis is limited. We aimed to assess the safety and efficacy of colistin for the treatment of VAP.

Methods. We searched MEDLINE and Cochrane Database of Systematic Reviews for studies comparing colistin vs other antibiotics for treatment of VAP in patients without cystic fibrosis. QUOROM guidelines were followed, the I² method was used for heterogeneity, and a random-effects model for odds ratio (OR) estimates.

Results. Six controlled studies met the inclusion criteria. Clinical response did not differ significantly between colistin and control groups (OR, 1.14; 95% confidence interval [CI], .74–1.77; P = .56; I² = 0%). The efficacy of colistin was independent of study design (prospective OR, 0.89 [95% CI, .48–1.66; P = .71; I² = 0%]; retrospective OR, 1.45 [95% CI, .79–2.68; P = .23; I² = 0%]; randomized trials OR, 0.86 [95% CI, 0.43–1.74; P = .68; I² = 0%]). There was no indication of a significant change in clinical response after controlling for concomitant antibiotic treatment (intercept, 0.121; slope, 0.0315; P = .95). Treatment with colistin vs controls did not affect hospital mortality (OR, 0.92; 95% CI, 0.50–1.67; P = .78; I² = 34.59%) or nephrotoxicity (OR, 1.14; 95% CI, 0.59–2.20; P = .69; I² = 0%). Fourteen single-arm studies have been analyzed, and the results were in concordance with the findings of the controlled studies.

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

The incidence of ventilator-associated pneumonia (VAP) is 10%–30% [1–3], with mortality rates ranging 24%–76%, and even higher mortality rate when the lung infection is caused by multidrug-resistant (MDR) pathogens [4]. More targeted antibiotic therapy may improve the cure rates and survival in patients with VAP [5–7]. The poor prognosis of these patients seems to be associated with inadequate initial antibiotic selection [8, 9], especially if the causative microorganisms are MDR. These gram-negative bacteria make the empiric choice of appropriate antimicrobial treatment difficult, and with the increasing prevalence of these organisms, colistin has recently become the focus of interest to clinicians.

Colistin, a natural substance produced by Bacillus polymyxa subspecies colistinus, is a cationic lipopeptide [6, 10, 11]. The hydrophilic and lipophilic moieties allow binding to the lipopolysaccharide molecules on the outer cell wall of gram-negative bacteria, displacing ions that stabilize the lipopolysaccharide molecules [6, 10, 12], leading to cell permeability changes, leakage of the cellular content, and cell death [6, 10, 11, 13]. Colistin sulfate and colistimethate sodium have been the commercially available forms. Both forms can be used for inhalation; colistimethate sodium is administered only parenterally, and colistin sulfate has been used orally.
or topically [6, 11]. Colistimethate sodium is considered to have fewer side effects and to be less potent than colistin and is more commonly used in clinical practice [11, 13, 14].

The effectiveness of intravenous colistin for treatment of lung infections has been debated because of its poor penetration into the pulmonary parenchyma [15]. Aerosolized colistin might be an alternative option for treatment of patients with VAP because the drug achieves high concentration in the respiratory tract while avoiding systemic effects [16]. Aerosolized colistin has been successfully used to prevent pulmonary exacerbation and lung deterioration in patients with cystic fibrosis (CF) colonized with *Pseudomonas aeruginosa* [16]. Colistin has been recommended in the most recent American Thoracic Society Guidelines as a therapeutic option for the treatment of VAP caused by MDR gram-negative organisms [17]. However, the experience with the use of colistin has been limited. The aim of our study was to systematically evaluate the published evidence regarding the safety and efficacy of intravenous and aerosolized colistin for the treatment of VAP.

**METHODS**

**Literature Search**

We searched PubMed, Embase, and Cochrane Library from their inception until February 2011 using the following key words: colistin, polymixin E, pneumonia, VAP, intravenous, aerosolized, nebulized, and inhaled. Two investigators (D. F. and C. M.) performed independently the literature search and the study selection. Any disagreement was resolved by a third author (A. K.), and a final consensus was reached among all authors.

**Study Selection**

Studies were considered eligible if they reported the safety and efficacy of intravenous and/or aerosolized colistin in the treatment of VAP. Aerosolized colistin could be used as adjunctive or solitary treatment. The studies that did not report treatment outcome and adverse effects of treatment with colistin and studies conducted in patients with CF were excluded. No language restrictions were applied. The QUOROM criteria were used for the search method (Figure 1).

**Data Extraction**

The following variables were collected from the studies: authors, publication year, study design, country where the study was performed, sex, age, sample size, diagnostic criteria for VAP, type and dose of colistin administered, route of administration, coadministration of other antibiotics, length of therapy, type of microorganism, susceptibility testing performed, underlying conditions, severity of illness (APACHE scores), outcomes (clinical and microbiological cure; length of intensive care and hospital stay; intensive care, 28-day, in hospital and VAP-attributable mortality), and reported toxicity (nephrotoxicity, neurotoxicity, respiratory adverse effects).

**Definitions**

Nephrotoxicity in patients with normal renal function was defined as increased serum creatinine values (>2 mg/dL), a 50% reduction in the calculated creatinine clearance compared with the baseline value, or need for renal replacement therapy [18–25]. Nephrotoxicity in patients with preexisting renal impairment was defined as a 50% increase of the baseline creatinine level, a 50% reduction in the calculated creatinine clearance compared with baseline, or a need for renal replacement therapy [18–25]. Pneumonia was considered VAP if the onset occurred ≥48 hours after intubation and the infection has not been incubating before; pneumonia was diagnosed on the basis of new or progressive pulmonary infiltrates and ≥2 of the following: fever >38°C or hypothermia <35.5°C, leukocytosis >12 000 cells/mL or leukopenia <4000 cells/mL, purulent bronchial secretions; if bronchoalveolar lavage was performed, ≥10^4 colony-forming units/mL were isolated in the culture [18–34]. Clinical response was defined as clinical cure or clinical improvement (complete or partial resolution, respectively, of the signs and symptoms of infection by the end of therapy) [19]. Microbiological response was defined as no growth of the causative pathogen at the end of therapy, regardless of the clinical outcome [19].

**Dose Standardization for the Study**

Because there is no standard formulation of colistimethate sodium used worldwide, the authors standardized the doses used to colistin base activity. Several articles reported the type of
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Type of Study</th>
<th>Sample Size, Colistin/Control, No. of Patients</th>
<th>Country</th>
<th>Colistin Manufacturer</th>
<th>Route of Administration</th>
<th>Organisms Isolated</th>
<th>Susceptibility Testing</th>
<th>Concomitant Antibiotics Administered</th>
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<tbody>
<tr>
<td>Kallel et al (2007) [32]</td>
<td>Retrospective, 2 arms</td>
<td>60/60</td>
<td>Tunisia</td>
<td>Bellon; Rhône-Poulenc (France)</td>
<td>Intravenous</td>
<td>Acinetobacter baumannii, Pseudomonas aeruginosa</td>
<td>Disk diffusion</td>
<td>No</td>
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<tr>
<td>Garnacho-Montero et al (2003) [18]</td>
<td>Prospective, 2 arms</td>
<td>21/14</td>
<td>Spain</td>
<td>Bellon; Rhône -Poulenc (France)</td>
<td>Intravenous</td>
<td>A. baumannii</td>
<td>Microdilution(\textsuperscript{a})</td>
<td>Microdilution(\textsuperscript{a})</td>
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<tr>
<td>Nakwan et al (2011) [33]</td>
<td>Retrospective, 2 arms</td>
<td>8/7</td>
<td>Thailand</td>
<td>Atlantic Pharmaceutical (Thailand)</td>
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<td>A. baumannii</td>
<td>Disk diffusion</td>
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<td>Rios et al (2007) [34]</td>
<td>Retrospective, 2 arms</td>
<td>31/30</td>
<td>Argentina</td>
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<td>Intravenous</td>
<td>A. baumannii, P. aeruginosa</td>
<td>Disk diffusion</td>
<td>Disk diffusion</td>
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<tr>
<td>Falagas et al (2006) [35]</td>
<td>Prospective, single arm</td>
<td>9/NA</td>
<td>Greece</td>
<td>Norma (Greece)</td>
<td>Intravenous + nebulized</td>
<td>Not available</td>
<td>E-test; disk diffusion</td>
<td>Broth microdilution (Organon Teknika)</td>
</tr>
<tr>
<td>Song et al (2008) [26]</td>
<td>Retrospective, single arm</td>
<td>10/NA</td>
<td>Korea</td>
<td>NA</td>
<td>Intravenous</td>
<td>A. baumannii</td>
<td>Agar dilution</td>
<td>Agar dilution; disk diffusion; E-test</td>
</tr>
<tr>
<td>Korbila et al (2010) [27]</td>
<td>Retrospective, single arm</td>
<td>121/NA</td>
<td>Greece</td>
<td>Forest Laboratories (United Kingdom); Norma (Greece)</td>
<td>Intravenous + nebulized; intravenous</td>
<td>A. baumannii, P. aeruginosa, K. pneumoniae</td>
<td>E-test; Mueller- Hinton agar</td>
<td>Microdilution(\textsuperscript{b})</td>
</tr>
<tr>
<td>Lin et al (2010) [28]</td>
<td>Retrospective, single arm</td>
<td>45/NA</td>
<td>Taiwan</td>
<td>TTY Biopharm (Taiwan)</td>
<td>Nebulized</td>
<td>A. baumannii</td>
<td>Disk diffusion; microdilution(\textsuperscript{b})</td>
<td>Disk diffusion; microdilution(\textsuperscript{b})</td>
</tr>
<tr>
<td>Mastoraki et al (2008) [20]</td>
<td>Prospective, single arm</td>
<td>8/NA</td>
<td>Greece</td>
<td>Norma (Greece)</td>
<td>Intravenous + nebulized</td>
<td>P. aeruginosa</td>
<td>Disk diffusion</td>
<td>E test</td>
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<tr>
<td>Iosifidis et al (2010) [39]</td>
<td>Retrospective, single arm</td>
<td>11/NA</td>
<td>Greece</td>
<td>Norma (Greece)</td>
<td>Intravenous</td>
<td>A. baumannii, P. aeruginosa, Enterobacter cloacae, K. pneumoniae</td>
<td>Disk diffusion</td>
<td>Microdilution(\textsuperscript{b}); disk diffusion</td>
</tr>
<tr>
<td>Author (Year)</td>
<td>Type of Study, Colistin/Control, No. of Patients</td>
<td>Country</td>
<td>Colistin Manufacturer</td>
<td>Route of Administration</td>
<td>Organisms Isolated</td>
<td>Susceptibility Testing</td>
<td>Concomitant Antibiotics Administered</td>
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<td>Retrospective, single arm</td>
<td>9/NA</td>
<td>Turkey</td>
<td>Intravenous</td>
<td>A. baumanii</td>
<td>Microdilution&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Bassetti et al (2008) [21]</td>
<td>Prospective, single arm</td>
<td>19/NA</td>
<td>Italy</td>
<td>Intravenous</td>
<td>A. baumanii</td>
<td>Agar dilution; disk diffusion</td>
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<tr>
<td>Michałopoulos et al (2008) [23]</td>
<td>Prospective, single arm</td>
<td>60/NA</td>
<td>Greece</td>
<td>Nebulized</td>
<td>A. baumanii</td>
<td>E-test (AB Biodisk)</td>
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<tr>
<td>Liden et al (2003) [22]</td>
<td>Prospective, single arm</td>
<td>18/NA</td>
<td>United States</td>
<td>Intravenous</td>
<td>P. aeruginosa</td>
<td>Disk diffusion; broth microdilution</td>
<td>Yes</td>
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<tr>
<td>Markou et al (2003) [31]</td>
<td>Prospective, single arm</td>
<td>15/NA</td>
<td>Greece</td>
<td>Intravenous</td>
<td>P. aeruginosa</td>
<td>Disk diffusion</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Markou et al (2008) [40]</td>
<td>Prospective, single arm</td>
<td>10/NA</td>
<td>Greece</td>
<td>Intravenous</td>
<td>P. aeruginosa</td>
<td>Not available</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

<sup>a</sup> Microscan system; Baxter Health Care.
<sup>b</sup> Vitek 2.
colistimethate sulfate derivative, the conversion to colistin base, and the name of manufacturer that was used. For the articles in which information was missing, the authors were contacted to provide the manufacturer, formulation, and dosing equivalence of colistin used. It has been reported that ~12500 IU colistimethate sodium is equivalent to 1 mg of colistimethate sodium and that ~2.67 mg of colistimethate sodium is equivalent to 1 mg of colistin base [6]. Depending on the manufacturer, it has also been reported that 1 mg of colistin base is equivalent to 2.4 mg of colistimethate sodium and 30000 IU of colistimethate sodium [35].

Statistical Analysis
The meta-analysis was conducted using metafor package for R developed by Wolfgang Viechtbauer [36]. The data were pooled using the DerSimonian and Laird random-effects model for single-arm and controlled studies [37]. The Q statistic method was used to assess statistical heterogeneity. For studies with no event of interest in a treatment group, 1.0 was added to all cells. For studies providing median and range only for continuous outcomes, mean value and variance were estimated using the median and range [38]. For 2-arm studies, binary outcomes results were expressed as odds ratios (ORs), and continuous outcomes results were expressed as mean difference between 2 groups. The I^2 method was used to assess the magnitude of variation secondary to heterogeneity. A meta-regression was performed to evaluate the influence of concomitant antibiotic treatment on the effectiveness of the colistin. Egger regression and Begg and Mazumdar methods were used to evaluate publication bias. Statistical power calculations were performed on the basis of the comparison of 2 independent proportions using the software PASS, version 2005 (Number Crunching Statistical Systems).

RESULTS
The single-arm analysis included 16 arms from 14 studies (437 patients) [19–23, 26–31, 35, 39, 40] and the controlled studies analysis included 6 studies (359 patients) [18, 24, 25, 32–34]. The 2-arm studies were unblinded and used similar definition for VAP. Characteristics of the studies included in the analyses are presented in Table 1. The mean APACHE scores were as follows: in the single-arm studies, 17.78 (standard deviation [SD], 4.10) [19, 21, 23, 26–31, 40]; in the 2-arm studies [18, 24, 25, 32, 34], for the colistin arm, 18.16 (SD, 2.45), for the control arm, 17.44 (SD, 2.5) (P = .75). In the 2-arm studies, aerosolized colistin [24, 33] was administered for a mean of 9.25 days (SD, 0.35) at a mean dose of 355 mg/70 kg/d (SD, 289.91), and intravenous form [18, 25, 32, 34] for a mean of 11.4 days (SD, 2.58) at a mean dose of 252.49 mg/70 kg/d (SD, 85.90). In the single-arm studies, aerosolized colistin [19, 20, 23, 27, 28, 30, 35] was administered for a mean of 13.93 days (SD, 2.28) at a mean dose of 80.03 mg/70 kg/d (SD, 32), and intravenous form [19–22, 26, 27, 29, 31, 35, 39, 40] for a mean of 14.98 days (SD, 4.56) at a mean dose of 209.58 mg/70 kg/d (SD, 80.08).

Controlled Studies Meta-analysis
Clinical Outcome
The overall clinical response did not differ significantly between colistin and control groups [18, 24, 25, 32–34] (OR, 1.14 [95% confidence interval (CI), 0.59–2.20; P = .69]; I^2 = 0%; Q = 3.14 [P = .53]) (Figure 3). The subgroup analysis is presented in Table 2. The meta-regression analysis showed no significant change in clinical response to colistin after controlling for concomitant antibiotic treatment (intercept, 0.121; slope, 0.0315; P = .66; I^2 = 5.46 to 10.73 days [P = .997]; and 28-day mortality (2 studies; 148 patients) [25, 32] (OR, 1.997 [95% CI, .97–4.12; P = .06]; I^2 = 2.48%; Q = 1.03 [P = .31]).

Mortality
No significant difference was noted when colistin was compared with controls with respect to hospital mortality (5 studies; 331 patients) [18, 24, 32–34] (OR, 0.92 [95% CI, .50–1.67; P = .78]; I^2 = 34.59%; Q = 6.12 [P = .19]); intensive care unit (ICU) mortality (2 studies; 155 patients) [18, 32] (OR, 1.27 [95% CI, .66–2.43; P = .47]; I^2 = 0%; Q = 0.057 [P = .81]); VAP-related death (2 studies; 135 patients) [18, 24] (OR, 1.11 [95% CI, .55–2.24; P = .77]; I^2 = 0%; Q = 0.00 [P = .997]); and 28-day mortality (2 studies; 148 patients) [25, 32] (OR, 1.62 [95% CI, .795–3.32; P = .18]; I^2 = 0%; Q = 0.0011 [P = .97]).

Length of Stay
The mean lengths of ICU stay (4 studies; 244 patients) [18, 25, 32] and hospital stay (2 studies; 96 patients) [18, 34] did not differ significantly between the colistin and control groups; the mean differences were 2.63 days (95% CI, −5.46 to 10.73 days [P = .52]; I^2 = 67%; Q = 9.0922 [P = .0281]) and 7.48 days (95% CI, −12.66 to 27.61 days [P = .47]; I^2 = 55.79%; Q = 2.2622 [P = .1326]).

Safety Analysis
Overall reported nephrotoxicity did not differ significantly between colistin and control groups (5 studies; 344 patients) [18, 24, 25, 32, 34] (OR, 1.14 [95% CI, 0.59–2.20; P = .69]; I^2 = 0%; Q = 3.14 [P = .53]) (Figure 3). The subgroup analysis for nephrotoxicity is presented in Table 3. Neurotoxicity did not differ significantly between the colistin and control...
group (3 studies; 183 patients) [18, 25, 32] (OR, 1.39 [95% CI, .17–11.61; P = .76]; I² = 0%; Q = 0.41; P = .82). Only 1 study evaluated the respiratory toxicity for colistin (4 of 51 patients) and control (1 of 49 patients) groups [24] (P = .36).

**Power Analysis**
The statistical power calculation was performed to determine if the overall sample size in controlled studies analyzed for efficacy (n = 359) would be large enough to detect a potential significant colistin superiority. We found that a total of n = 360 would achieve 74% power to detect 13% difference in clinical response rate between the colistin and control groups at the .05 level of significance. Thus, our efficacy meta-analysis sample size (n = 359) was not adequate but close to achieving 80% power to detect colistin superiority.

**Table 2. Subgroup Analysis of Clinical Response With Colistin Versus Control Antibiotics for Treatment of Ventilator-Associated Pneumonia in Controlled Studies**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Studies, No. (Patients, No.)</th>
<th>Efficacy of Colistin Compared With Control OR [95% CI; P]</th>
<th>Heterogeneity of Studies Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients only</td>
<td>5 (344)</td>
<td>1.06 (.68–1.66); P = .81</td>
<td>I² = 0%; Q = 0.82; P = .96</td>
</tr>
<tr>
<td>By route of administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>4 (244)</td>
<td>1.13 (.66–1.93); P = .66</td>
<td>I² = 0%; Q = 0.64; P = .89</td>
</tr>
<tr>
<td>Aerosolized</td>
<td>2 (115)</td>
<td>3.02 (1.8–51.19); P = .44</td>
<td>I² = 76.9%; Q = 4.33; P = .04</td>
</tr>
<tr>
<td>By study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>3 (162)</td>
<td>0.89 (.48–1.66); P = .71</td>
<td>I² = 0%</td>
</tr>
<tr>
<td>Retrospective</td>
<td>3 (196)</td>
<td>1.45 (.79–2.68); P = .23</td>
<td>I² = 0%</td>
</tr>
<tr>
<td>Randomized</td>
<td>2 (128)</td>
<td>0.86 (.43–1.74); P = .68</td>
<td>I² = 0%</td>
</tr>
<tr>
<td>By geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>3 (183)</td>
<td>1.04 (.55–1.96); P = .91</td>
<td>I² = 0%; Q = 0.41; P = .81</td>
</tr>
<tr>
<td>Asia</td>
<td>2 (115)</td>
<td>3.02 (1.18–51.19); P = .44</td>
<td>I² = 76.9%; Q = 4.33; P = .04</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
Single-Arm Studies Meta-analysis

Clinical Outcome
The favorable clinical response with colistin (15 arms from 13 studies; 429 patients) [19, 21–23, 26–31, 35, 39, 40] was 72% (95% CI, .64–.80; Q = 55.3; P = .0001). The subgroup analysis of clinical response is presented in Table 4.

Microbiological Outcome
The overall microbiological response rate (10 arms from 9 studies; 267 patients) [19, 20, 22, 23, 26, 28–31] was 61% (95% CI, .44–.79; Q = 121.56; P < .0001). By the route of administration, microbiological cure rate was 46% (95% CI, .36–.57; Q = 4.56; P = .34) for the intravenous form (5 studies; 95 patients) [19, 22, 26, 29, 31] and 73% (95% CI, .43–.99; Q = 51.2; P < .0001) for the aerosolized form (3 studies; 121 patients) [23, 28, 30].

Mortality
The in-hospital mortality rate (12 arms from 11 studies; 334 patients) [21–23, 26–31, 39, 40] was 34% (95% CI, .23–.45; Q = 62.85; P < .0001). The ICU mortality rate (7 arms from 5 studies; 257 patients) [19, 21, 27, 30, 31] was 29% (95% CI, .15–.42; Q = 43.61; P < .0001). The 28-day mortality rate (5 arms from 4 studies; 166 patients) [21, 26, 27, 30] was 25%

<table>
<thead>
<tr>
<th>Variables</th>
<th>Studies, No. (Patients, No.)</th>
<th>Nephrotoxicity of Colistin Compared With Controls, OR (95% CI)</th>
<th>Heterogeneity of Studies Included</th>
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</thead>
<tbody>
<tr>
<td>Adult studies only</td>
<td>5 (344)</td>
<td>1.14 (.59–2.20); P = .69</td>
<td>I^2 = 0%</td>
</tr>
<tr>
<td>Intravenous administration</td>
<td>4 (244)</td>
<td>1.17 (.38–3.55); P = .79</td>
<td>I^2 = 23.91%</td>
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<tr>
<td>By study design</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prospective</td>
<td>3 (163)</td>
<td>1.04 (.49–2.20); P = .92</td>
<td>I^2 = 5.39%</td>
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<tr>
<td>Retrospective</td>
<td>2 (181)</td>
<td>1.83 (.36–9.26); P = .46</td>
<td>I^2 = 0%</td>
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<tr>
<td>Randomized</td>
<td>2 (128)</td>
<td>1.40 (.61–3.19); P = .43</td>
<td>I^2 = 0%</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
The overall nephrotoxicity rate (11 arms from 10 studies; 329 patients) [19, 20, 23, 27, 28, 29, 31, 39] was 14% (95% CI, .07-.22; Q = 15.02; P = .02).

Length of Stay
The mean length of ICU stay (7 arms from 6 studies; 237 patients) [19, 21-23, 28, 29] was 34.46 days (range, 25.64–43.28 days; Q = 103.47; P < .0001). The mean length of hospital stay (3 studies; 82 patients) [21, 22, 28] was 70.91 days (range, 34.18–107.64 days; Q = 50.08; P < .0001).

Safety Analysis
The overall nephrotoxicity rate (11 arms from 10 studies; 270 patients) [19, 20, 23, 26, 28–31, 39, 40] was 5.7% (95% CI, .02-.09; Q = 22.43; P = .01). Subgroup analysis for nephrotoxicity is presented in Table 5. Although nephrotoxicity was higher in the intravenous administration than combined intravenous-aerosolized administration, there was no significant difference in the intravenous dose of colistin used (mean, 191.74 mg/70 kg/d [SD, 109.33] vs 281.26 mg/70 kg/d [SD, 0]; P = .6). No patients had neurotoxicity or respiratory side effects in the 8 arms from 7 studies (234 patients) [19, 20, 23, 28, 29, 31, 39] that investigated neurotoxicity and the 8 arms from 6 studies (329 patients) [19, 20, 23, 27–29] that investigated respiratory toxicity.

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DISCUSSION

The treatment of VAP caused by MDR gram-negative organisms with intravenous and/or adjunctive aerosolized colistin was as effective as with other antibiotics in the control group. Clinical response did not change significantly even after controlling for concomitant antibiotic treatment and for the administration route of colistin. Further, we noticed very low between-study heterogeneity for intravenous colistin route but not for aerosolized colistin route. There was no significant difference between colistin and control groups with regard to mortality, emergence of resistance, or toxicity. APACHE score is a validated tool to measure severity of illness; the higher the APACHE score, the poorer the clinical response and the higher the mortality in critically ill patients [27, 41]. The balanced APACHE scores between groups in our study brought more strength to our comparison analyses. The all-cause mortality for patients treated with colistin did not differ significantly from those of the patients treated with other antibiotics and were in agreement with those reported elsewhere in the literature for VAP [4]. In a recent study by Paul et al [42] that included patients with various infections, treatment with colistin was associated with higher mortality, a statistically significant difference in the subgroup of patients with bacteremia. We have to consider that the infections in this study were heterogeneous, although our study included only patients with VAP. The results of the single-arm studies analysis were also in concordance with those findings from the controlled studies meta-analysis.

The OR for efficacy with adjunctive aerosolized colistin was greater than that seen with the intravenous colistin, but the differences were not statistically significant. Adjunctive aerosolized colistin seems to be an attractive treatment options for patients with VAP, because it achieves high lung concentrations without significant systemic absorption and toxicity [16, 43].

The small differences between clinical and microbiological outcomes in our meta-analysis might be secondary to the
persistent colonization of the lungs with the infecting organisms or to the different lung concentrations achieved by different routes of administration, or both. From the data previously published, it seems that aerosolized colistin might reduce sputum bacterial growth and improve the microbiological outcomes [16, 24, 33]. Most published experience with inhaled colistin comes from the CF literature [43–45]. Because effective antibiotic treatment of VAP depends on adequate delivery of antimicrobial agents to the lung, we have to pay attention to the doses of the antibiotic administered, to the route of administration, and to the pharmacodynamic characteristics of each agent. No significant number of colistin-resistant pathogens was reported after inhaled treatment in the studies included in this meta-analysis [20, 28, 30, 33]. However, the aerosolized colistin treatment duration for VAP in this meta-analysis was shorter than the 4-week regimen commonly administered to patients with CF, in whom emergence of bacterial resistance has been reported [46].

We noted a significant difference in the mean dose of colistin used in aerosolized form among the studies. Colistin is a concentration-dependent drug, and the area under the curve/minimum inhibitory concentration ratio (AUC/MIC) best correlate with its efficacy. For example, optimal bactericidal effects against P. aeruginosa were observed when AUC/MIC ∼ 30 [47]. There is minimal pharmacokinetic data available for colistin in the sputum. Ratjen et al [16] showed in patients with CF that 66 mg of colistin base produced peak sputum concentrations of 40 mg/L 1.5 hour after inhalation and remained >4 mg/L after 12 hours; however, no data on the AUC in the sputum was provided. The optimal dose of aerosolized colistin to maximize the effect on clinical and microbiological outcome is yet to be determined.

In our study, colistin was associated with a relatively low rate of renal dysfunction, a rate that did not change significantly when we adjusted for age or for the route of administration. The nephrotoxicity rate for colistin was similar to that in the control group. Other published reports [18, 20, 23–26, 28, 31–34, 48] do not corroborate the original association of increased rate of renal failure with colistin administration [49, 50], whereas other reports confirm it [42]. However, renal function should be closely monitored during colistin administration, and the dose should be changed in case of renal impairment. We did not find an increased risk of neurotoxicity with colistin in our study, although neurotoxicity, including motor and sensory deficits, seizures, and mental status changes, has been reported in the past, especially in patients with renal impairment [49, 50]. Moreover, there was no significant lung toxicity noted in the studies included in our meta-analysis.

We noticed variation of the outcomes by geographic region that could be explained by differences in practice among different countries. The vials of various formulations available on the market are labeled differently with regard to content; the recommended dose for the product varies accordingly [43]. These differences would make comparison of the published data difficult without conversion to the same common units, which was appropriately performed in our study. Because there is no standardization of colistin formulation and dosing, there is potential for underdosing of colistin in some studies reflected as lower clinical response rate but also lower toxicity.

Our study has limitations and strengths. First, there was variability in the quality of the studies, with some inter-study heterogeneity. Second, there was variability in the methods and interpretation of susceptibility testing used among the studies. The study’s strengths include: the rigorous design, the sample
size, the relative uniform definition of VAP used, and the homogeneity of the population (APACHE score).

CONCLUSION

Our data show that colistin can be a safe and effective alternative therapy for VAP caused by MDR gram-negative organisms. We do not suggest that colistin should be used as first-line therapy for VAP caused by MDR gram-negative organism; it should be considered as an alternative option once the susceptibility results are available. The 72% favorable clinical response rate and 34% in-hospital mortality rate with colistin therapy were within the range of clinical response and mortality rates reported in the literature.

Notes

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References


