

## ORIGINAL

# Nebulized colistin treatment of multi-resistant *Acinetobacter baumannii* pulmonary infection in critical ill patients

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Received 14 October 2010; accepted 19 January 2011

### KEYWORDS

Colistin;  
Nebulized colistin;  
Multi-resistant germs;  
*Acinetobacter baumannii*

### Abstract

**Objective:** To analyze the efficacy of nebulized colistin in the microbiological eradication and clinical improvement of patients with pulmonary infection by multi-resistant *Acinetobacter baumannii* (MAB).

**Design:** A retrospective study.

**Setting:** Intensive Care Unit of a Tertiary hospital.

**Patients:** Hospitalized patients on invasive mechanical ventilation with positive MAB cultures of the airway.

**Interventions:** All received treatment with colistin (CL). Nosocomial pneumonia (NP) or Tracheobronchitis (TB) was determined according to routine criteria and colonization (CO) was determined in the case of a positive culture in the absence of infection criteria. Three groups of patients were defined: those treated with nebulized CL, those treated with IV CL and those treated with IV CL plus nebulized CL.

**Main measurements:** Baseline characteristics. Microbiological eradication and clinical recovery were evaluated according to routine criteria.

**Results:** 83 patients were studied, 54 of whom were treated, with the following diagnoses: 15 (27.8%) with NP, 16 (29.6%) with TB and 23 patients (42.6%) with CO. Nebulized CL was used in 36 patients (66.7%); 66.7% of which for CO, 33.3% in treatment for TB and in no case of NP. In 61.1% of the patients, IV CL was used: 22.2% of which for CO, 38.9% for TB and 38.9% in NP. The combination of IV CL and nebulized CL was used in 15 patients (27.8%): 5 patients (33.3%) CO, 2 patients (13.3%) TB and 8 patients (53.3%) NP. Microbiological eradication was achieved in 32 patients (59.3%), with the following distribution: 8 (47.1%) with IV CL, 15 (83.3%) with nebulized CL and 9 patients (69.2%) with a combination of IV CL and nebulized CL. Clinical recovery was achieved in 42 patients (77.8%): 12 (80%) with IV CL, 18 (94.7%) with nebulized CL and 12 (85.7%) with a combination of nebulized and IV CL. These differences were not significant. In

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the group of patients with infection due to TB and NP (31 patients, 57.4%), microbiological eradication was achieved in 5 patients (100%) treated with nebulized CL and in 6 of the 9 patients (42.9%) treated with IV CL, the difference being significant ( $P < .05$ ). Clinical recovery in this group was 100% (6 patients) treated with nebulized CL and 75% (9 of the 12 patients) in the IV CL group. This difference was not significant.

**Conclusions:** Our study suggests that treatment with colistin in patients with pulmonary infection with multi-resistant *Acinetobacter baumannii* could be more efficient if it were to be administered solely nebulized or in combination with IV colistin rather than administered solely intravenously.

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## PALABRAS CLAVE

Colistina;  
Colistina nebulizada;  
Microorganismos  
multirresistentes;  
*Acinetobacter  
baumannii*

## Utilización de la colistina nebulizada en la colonización e infección respiratoria por *Acinetobacter baumannii* en pacientes críticos

### Resumen

**Objetivo:** Evaluar la eficacia de la colistina nebulizada en la erradicación microbiológica y la mejoría clínica de pacientes con *Acinetobacter baumannii* en vías respiratorias.

**Diseño:** Estudio retrospectivo.

**Ámbito:** Servicio de medicina intensiva en hospital terciario.

**Pacientes:** Pacientes ingresados en ventilación mecánica invasiva con cultivos positivos en vía aérea para *A. baumannii* multirresistente.

**Intervenciones:** Todos recibieron tratamiento con colistina (CL). Se determinó neumonía nosocomial (NN) o traqueobronquitis (TB) según criterios habituales y colonización (CO) si había cultivo positivo en ausencia de criterios de infección. Se definieron 3 grupos de pacientes: tratados con CL nebulizada, con CL i.v. y con CL i.v. más nebulizada.

**Variables de interés:** Características basales. Se consideró erradicación microbiológica y curación clínica según criterios habituales.

**Resultados:** Se estudió a 83 pacientes; 54 fueron tratados, con los diagnósticos: 15 (27,8%) con NN, 16 (29,6%) con TB y 23 pacientes (42,6%) con CO. La CL nebulizada fue utilizada en 36 pacientes (66,7%): en el 66,7% en CO, el 33,3% en tratamiento de TB y en ningún caso de NN. En el 61,1% de los pacientes se utilizó CL i.v.: en la CO en el 22,2%, en la TB en el 38,9% y en las NN en el 38,9%. La combinación de CL i.v. más nebulizada fue utilizada en 15 pacientes (27,8%), que se empleó: 5 (33,3%) CO, 2 (13,3%) TB y 8 (53,3%) NN. La erradicación microbiológica se consiguió en 32 pacientes (59,3%), con la distribución: 8 (47,1%) con CL i.v., 15 (83,3%) con CL nebulizadas y 9 pacientes (69,2%) con la combinación de CL i.v. más nebulizada. La curación clínica se consigue en 42 pacientes (77,8%): 12 (80%) con CL i.v., 18 (94,7%) con CL nebulizada y 12 (85,7%) con la combinación de CL nebulizada e intravenosa. Estas diferencias no fueron significativas. En el grupo de pacientes con infección por TB y NN (31 pacientes, 57,4%) la erradicación microbiológica se consiguió en 5 pacientes (100%) tratados con CL nebulizada y en 6 de 14 (42,9%) tratados con CL i.v.; esta diferencia fue significativa ( $p < 0,05$ ). La curación clínica en este grupo fue del 100% (6 pacientes) tratados con CL nebulizada y del 75% (9 de 12) en el grupo de CL i.v. Esta diferencia no fue significativa.

**Conclusiones:** Nuestro estudio señala que el tratamiento con colistina en pacientes con infección pulmonar por *A. baumannii* multirresistente podría ser más eficaz si se administra nebulizada o en combinación con colistina i.v. que si se administra de forma intravenosa solamente.

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## Introduction

Nosocomial colonization and infection caused by multiresistant gramnegative bacilli have increased greatly in recent years, and represent one of the most serious complications in patients admitted to the Intensive Care Unit (ICU). Among the different multiresistant gramnegative microorganisms, Special mention must be made of *Acinetobacter baumannii*.<sup>1</sup>

The antibiotic colistin was widely used between the 1960s and 1980s due to its potent bactericidal action, low incidence

of resistances, and excellent activity against gramnegative bacilli, including multiresistant strains. However, the associated toxicity (nephrotoxicity and neurotoxicity) eventually caused use of the drug to be abandoned.<sup>2</sup> In the 1980s, colistin began to be used via the nebulized route in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*.<sup>3</sup> On the other hand, the emergence of infections due to *A. baumannii* in critical patients has returned this antibiotic to the front line in clinical practice.

There is evidence that nebulized colistin in conjunction with the intravenous route could be useful for the treatment

of *A. baumannii* and *P. aeruginosa* infections.<sup>4</sup> The present study describes our experience with the use of nebulized colistin for the treatment of respiratory colonization and infection caused by *A. baumannii* in critical patients. The aim is to evaluate the efficacy of nebulized colistin in the clinical eradication and/or clinical improvement (in the context of tracheobronchitis and/or nosocomial pneumonia) of patients with *A. baumannii* isolated from airway cultures.

## Material and method

A retrospective study was made in the Department of Intensive Care Medicine of Virgen de la Salud Hospital in Toledo (Spain). We included all patients with *A. baumannii* positive airway sample cultures (tracheobronchial aspirate) at any time during admission, and who received treatment with colistin. All patients were subjected to mechanical ventilation, though at the time of the diagnosis some of them had already been weaned from the ventilator (11 patients; 20.4%) –with tracheotomy in all cases.

Colistin was administered via the intravenous route, nebulized, or via both routes simultaneously (mixed). The intravenous dose was adjusted according to renal function. The clinician in turn decided the dose of nebulized colistin, using three regimens: 10<sup>6</sup> IU/ 8 h, 5 x 10<sup>5</sup> IU/ 6 h and 10<sup>6</sup> IU/ 12 h. The patients were divided into three clinical groups:

- Nosocomial pneumonia (NP): diagnosis 48 hours after admission, based on the following criteria: new radiological infiltrates or progression of already existing infiltrates, fever > 38°C without any other explaining cause, leukocytosis ( $\geq 12,000/\mu\text{l}$ ) or leukopenia ( $< 4000/\mu\text{l}$ ), purulent sputum or increased bronchial secretion. Microbiological confirmation of the diagnosis was made based on positive respiratory sample cultures (bronchial aspirate) with a significant bacterial count ( $\geq 100,000$  cfu/ml).
- Tracheobronchitis (TB): fever > 38°C without any other explaining cause, leukocytosis ( $\geq 12,000/\mu\text{l}$ ) or leukopenia ( $< 4000/\mu\text{l}$ ) and purulent sputum or increased bronchial secretion without radiological infiltrates indicative of pneumonia. Microbiological confirmation of the diagnosis was made based on positive respiratory sample cultures (bronchial aspirate) ( $\geq 100,000$  cfu/ml).
- Colonization: positive culture in the absence of criteria of infection.

Colonized patients are not usually treated with antibiotics. The included colonized individuals were of two kinds: patients diagnosed with infection (and the decision to provide treatment therefore had been taken), and patients who upon review were regarded as being only colonized, since they did not meet the diagnostic criteria for pneumonia or tracheobronchitis. On the other hand, we included some colonized patients treated according to the criterion of the supervising physician, on the grounds that the treatment of colonization by multiresistant microorganisms is warranted in certain circumstances (e.g., in patients with cystic fibrosis colonized by *Pseudomonas*).<sup>3</sup>

The patients were evaluated for microbiological eradication and clinical recovery. The latter was defined by disappearance of the fever, normalization of the leukocyte counts, disappearance or significant improvement of the radiological infiltrates in the case of pneumonia, and disappearance or significant improvement of the bronchial secretions in the case of tracheobronchitis. Microbiological eradication in turn was defined by negative conversion of the respiratory sample culture in at least two consecutive cultures. Vigilance cultures were conducted on a weekly basis.

## Statistical analysis

Qualitative variables are presented as absolute values (percentages), while quantitative variables are reported as the mean  $\pm$  standard deviation (SD). The comparison of categorical variables was based on the chi-squared test, with the Fisher exact test in 2 x 2 groups. The comparison of quantitative variables in turn was carried out with the Mann-Whitney U-test. Statistical significance was considered for  $p < 0.05$ . The SPSS version 15.0 statistical package was used throughout (SPSS Inc., Chicago, IL, USA).

## Results

We reviewed a total of 83 patients with positive cultures for colistin-sensitive *A. baumannii* in bronchial secretions. Patients considered by the clinician to be colonized and who therefore received no antibiotic treatment were excluded. A total of 54 subjects were treated with colistin and included in the study. Their baseline characteristics, including the severity and multiorgan dysfunction scores at the time of the diagnosis of colonization or infection, are reported in Table 1. The most frequent causes of admission were: polytraumatism, 17 patients (31.5%); stroke, 10 patients (18.6%); septic shock, 10 patients (18.5%) and pneumonia, 8 patients (14.9%).

A total of 42.6% of the patients were colonized by *A. baumannii*; 29.6% presented tracheobronchitis and 27.8% pneumonia attributable to this organism. In 35.2% of the cases *A. baumannii* was the only microorganism isolated from the respiratory tract. The most frequently associated microorganisms were: *Klebsiella* (2), *E. coli* (1), *E. faecium* (1) and *Pseudomonas* [1]. In 46.3% of the cases colistin was administered as only antibiotic –the most frequently associated antibiotic drugs being meropenem (7 cases), aminoglycosides (6 cases), linezolid (4 cases), cefotaxime / ceftriaxone (3 cases), and piperacillin / tazobactam (3 cases).

The nebulized colistin dose was 10<sup>6</sup> IU/ 8 h in 33.3% of the cases, 5 x 10<sup>5</sup> IU/ 6 h in 14.8% and 10<sup>6</sup> IU/ 12 h in 14.8%. No patient developed erythema. In 14.8% of the patients corticosteroid premedication was provided, and in no case did bronchospasm occur when colistin was used in nebulized form. Four patients (7%) developed nephrotoxicity attributable to colistin. Table 1 also reports the different variables according to the type of colistin administered to the patient.

Microbiological eradication was achieved in 32 patients (59.3%). Specifically, eradication was achieved in 47% of the

**Table 1** General characteristics of the patients and distribution of the variables according to the type of colistin administered

	Total (n = 54)	Intravenous colistin (n = 18)	Nebulized colistin (n = 21)	Mixed colistin (n = 15)
Males	43 (79.6%)	15 (83.3%)	16 (76.2%)	12 (80%)
Age (years)	57.1 ± 17.6	60.1 ± 17.4	55.5 ± 19.8	55.6 ± 14.8
APACHE II	12.6 ± 5.3	12.8 ± 5.7	11.2 ± 4.3	14.1 ± 5.7
SOFA	4.4 ± 2.2	4.6 ± 2	3.7 ± 2	4.9 ± 2.4
Mechanical ventilation	43 (79.6%)	15 (83.3%)	14 (66.7%)	14 (93.3%)
Clinical diagnosis <sup>a,b</sup>				
Colonization	23 (42.6%)	4 (22.2%)	14 (66.7%)	5 (33.3%)
Tracheobronchitis	16 (29.6%)	7 (38.9%)	7 (33.3%)	2 (13.3%)
NP	15 (27.8%)	7 (38.9%)	0	8 (53.3%)
Stay in ICU (days)	46.8 ± 34.3	45.5 ± 36.5	49 ± 40.2	45.3 ± 22.7
Hospital stay (days)	66.1 ± 54.1	64.1 ± 63	70.9 ± 59	61.9 ± 35
Nephrotoxicity	4 (7.4%)	2 (11.1%)	1 (4.8%)	1 (6.7%)
Microbiological eradication	32 (59.3%)	8 (47.1%)	15 (83.3%)	9 (69.2%)
Clinical recovery	42 (77.8%)	12 (66.6%)	18 (85.7%)	12 (80%)
Death	12 (22.2%)	5 (27.8%)	4 (19%)	2 (20%)

NP: nosocomial pneumonia.

<sup>a</sup>In relation to *A. Baumannii*.<sup>b</sup>p < 0.05 among the three colistin administration groups.

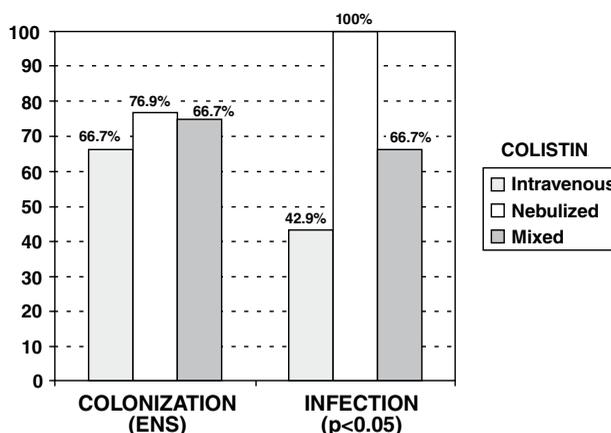
patients treated with intravenous colistin and in 83.3% of those treated with nebulized colistin only. The difference between these two groups was significant ( $p < 0.05$ ). On analyzing the colonization group (23 patients), microbiological eradication was achieved in 76.9% of the patients treated with nebulized colistin, in 75% of those administered mixed colistin, and in 66.7% of the patients treated with intravenous colistin – the differences in this case being nonsignificant. In the patients with tracheobronchitis and pneumonia (31 patients), microbiological eradication was achieved in 100% of the patients administered nebulized colistin, in 66.7% of those administered mixed colistin, and in 42.9% of the patients treated with intravenous colistin. In this case the difference between nebulized and intravenous colistin proved significant ( $p < 0.05$ ) (Fig. 1).

Clinical recovery was evidently analyzed only in the group with respiratory infection (tracheobronchitis and pneumonia), and occurred in 24 patients (85.7% of the total patients studied). Clinical recovery occurred in 100% of the 6 patients treated with nebulized colistin only (all diagnosed with tracheobronchitis), in 90% of those treated with mixed colistin, and in 75% of those treated with intravenous colistin – no statistically significant differences being observed among these groups.

## Discussion

Of the different nosocomial infections seen in the Intensive Care Unit, special mention must be made of respiratory infections in patients subjected to mechanical ventilation, in view of their important frequency and repercussions. The

growing emergence of multiresistant microorganisms such as *A. baumannii* and *P. aeruginosa* complicates the treatment of patients with infections associated to mechanical ventilation (pneumonia and tracheobronchitis), and has led to a change in the approach to treatment and the utilization of antibiotics such as colistin. The guides of the American Thoracic Society (ATS) indicate that antibiotics in aerosol can be used for the treatment of infections caused by microorganisms with a high minimum inhibitory concentration (MIC) and which are resistant to systemic treatments.<sup>5</sup>



**Figure 1** Microbiological eradication. Percentage of eradications in colonized and infected patients (tracheobronchitis and nosocomial pneumonia).

Colistin (polymyxin B) is an antibiotic of great bactericidal capacity with concentration-dependent activity in application to gram-negative bacilli, including multi-resistant strains. Following its discovery in the 1940s, colistin use peaked in the 1960s, followed by abandonment of its administration due to the associated neurotoxicity and nephrotoxicity. In the 1980s the drug was reintroduced in nebulized form for the treatment of patients with cystic fibrosis colonized by *P. aeruginosa*, in view of the good results obtained in these cases.<sup>3,4</sup> The aerosol administration of antibiotics is now being seen as a beneficial form of treatment in patients with respiratory infection.<sup>6</sup> This is mainly due to the high drug concentrations reached in the respiratory tract. In effect, the administration of two million nebulized units reaches peak sputum concentration within one hour –this being over 10 times higher than the MIC of *P. aeruginosa* and *A. baumannii*. Posteriorly, the concentration decreases, but maintains an average of 4 µg/ml 12 hours after administration, with low systemic concentrations.<sup>3</sup> In this way, nebulized or aerosol administration would allow a reduction of the drug doses used in intravenous antibiotherapy, by depositing the drug directly in the site of infection. The blood concentrations in turn would be reduced, together with the toxic side effects of colistin.<sup>7</sup> At present, when using the nebulized route, the recommended dose is 500,000 units/ 12 h for patients weighing under 40 kg, and one million units/ 8-12 h for those weighing over 80 kg. In the case of recurrent infections, the recommendation would be two million units every 8 hours.<sup>8,9</sup> The main inconvenience of the aerosol formulation is the potential induction of local side effects such as bronchoconstriction.<sup>6</sup>

In October 2009, Qin Lu et al. published an experimental study in pigs involving the induction of ventilator-associated pneumonia due to *P. aeruginosa* with a MIC for colistin < 2 µg/ml.<sup>10</sup> The animals were treated with nebulized or intravenous colistin, and were sacrificed 48 hours after the treatment. In the aerosol group the mean peak concentration in lung tissue was 2.8 µg/g. In the pigs treated with intravenous colistin, the colistin concentrations in lung tissue were undetectable. The authors concluded that nebulized colistin offers rapid and effective bactericidal action, and proposed the conduction of studies warranting its use in patients with pneumonia, as well as its combination with the intravenous route in patients with bacteremic pneumonia. These data had been correlated to clinical data from previous years.

In this context, in 2005, Kwa et al. published a retrospective study involving 21 patients with pneumonia due to *A. baumannii* and *P. aeruginosa*. They reviewed the patients treated with nebulized colistin and recorded a microbiological eradication rate of 85.7% and a clinical recovery rate of 57.1%.<sup>11</sup> In 2007, Pereira et al. used inhalatory colistin in 14 patients with pneumonia in which previous treatment with intravenous colistin had failed, and in another 5 patients diagnosed with tracheobronchitis<sup>12</sup> – all of them with colistin-sensitive gram-negative bacilli. The patients with pneumonia were jointly treated with intravenous and nebulized colistin, while the patients with tracheobronchitis received only nebulized colistin; 93% of the pneumonias met criteria of clinical recovery at the end of treatment, and 100% of the cases of tracheobronchitis

were healed. In 2008, Michalopoulos et al. used nebulized colistin to treat 60 critical patients diagnosed with pneumonia caused by *A. baumannii*, *P. aeruginosa* and *Klebsiella pneumoniae*; 57 of the patients also received systemic treatment.<sup>13</sup> The authors observed clinical recovery and microbiological eradication in 83.3% of the cases, and concluded that nebulized colistin can be regarded as an adjuvant to intravenous administration in pneumonias caused by colistin-sensitive microorganisms in critical patients. Likewise in 2008, Fagalas et al. published a series of 5 patients with nosocomial pneumonia due to *A. baumannii* and *P. aeruginosa* treated only with nebulized colistin and without adjunctive intravenous therapy. Four of the 5 patients (80%) recovered and survived.<sup>14</sup> The authors concluded that treatment with nebulized colistin alone in application to pneumonias caused by microorganisms that are sensitive to this drug deserves to be studied more in depth. In 2009, Korbila et al. published a retrospective study of 78 patients with ventilator-associated pneumonia treated with intravenous plus nebulized colistin, versus 43 patients treated with the intravenous formulation only.<sup>15</sup> Clinical recovery was recorded in 79.5% of the patients in the first group and in 60.5% of the patients treated with intravenous colistin only –the difference being statistically significant ( $p < 0.025$ ).

Our study shows colistin in mixed administration (nebulized and intravenous) to be superior for the treatment of respiratory infection due to *A. baumannii* than intravenous treatment only. The use of nebulized colistin, alone or in combination, improved the results in terms of microbiological eradication and clinical recovery in all the treatment groups.

Our study has clear limitations, including its retrospective nature and the limited number of patients in each group. Another limitation is the use of different dosing regimens. The regimen was decided by the physician treating the patient, and was independent of the nosologic characteristics of the case (colonization, tracheobronchitis or pneumonia). The existing literature describes different dosing regimens, though none have been shown to be superior to the rest. Nevertheless, we feel the regimen used to be representative of our clinical experience in the daily use of nebulized colistin in patients of this kind.<sup>16</sup>

Special mention should be made of the group of patients with tracheobronchitis treated with nebulized colistin only. The 5 patients recovered, and microbiological eradication was achieved in all of them, while in contrast in the group of subjects treated via the intravenous route, only three out of 5 recovered (60%). These data are not statistically significant, due to the small number of patients involved, though despite the limitations of our study, the results suggest that nebulized colistin alone should be viewed as an alternative for the treatment of these patients.

In our series, the patients treated with nebulized colistin achieved a significantly higher microbiological eradication rate than the group subjected to intravenous treatment. The cases diagnosed with pneumonia also achieved better results with combination treatment than with intravenous dosing alone. The infected patients who all recovered (100%) with nebulized colistin all presented tracheobronchitis; no patient diagnosed with pneumonia was treated with nebulized colistin only. On jointly considering all the patients with infection, i.e., tracheobronchitis and

pneumonia, the microbiological eradication rate was likewise significantly favorable to the group with nebulized colistin versus those administered intravenous colistin only.

In conclusion, our data coincide with those found in the literature: treatment with inhalatory colistin improves the results in patients with respiratory infections produced by *A. baumannii*. Despite the limitations of our study, we feel that inhalatory colistin should be regarded as an adjunct to intravenous dosing of the drug in patients with nosocomial pneumonia due to *A. baumannii*. Colistin administration in nebulized form only, without associated intravenous therapy, could be an alternative in patients with tracheobronchitis, or might possibly be the treatment of choice for securing microbiological eradication in colonized patients.

## Conflict of interest

The authors declare no conflict of interest.

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