

# Nebulized Colistin And Continuous Cyclic Azithromycin In Severe COPD Patients With Chronic Bronchial Infection Due To *Pseudomonas aeruginosa*: A Retrospective Cohort Study

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Concepción Montón<sup>1,2</sup>  
Elena Prina<sup>1</sup>  
Xavier Pomares<sup>1,3</sup>  
Jose R Cugat<sup>4</sup>  
Antonio Casabella<sup>5</sup>  
Joan Carles Oliva<sup>6</sup>  
Miguel Gallego<sup>1,3</sup>  
Eduard Monsó<sup>1,3</sup>

<sup>1</sup>Department of Respiratory Medicine, Hospital De Sabadell, Institut Universitari Parc Taulí-UAB, Sabadell, Spain; <sup>2</sup>Health Services Research on Chronic Diseases Network-REDISSEC, Galdakao, Spain; <sup>3</sup>CIBER de Enfermedades Respiratorias, CIBERES, Madrid, Spain; <sup>4</sup>Department of Respiratory Medicine, Fundació Althaia, Manresa, Spain; <sup>5</sup>Laboratory of Microbiology-UDIAT, Institut Universitari Parc Taulí-UAB, Sabadell, Spain; <sup>6</sup>Epidemiology and Assessment Unit, Fundació Parc Taulí, Universitat Autònoma de Barcelona, Sabadell, Spain

**Introduction:** Long-term use of nebulized or oral antibiotics is common in the treatment of cystic fibrosis and non-cystic fibrosis bronchiectasis. To date, however, few studies have focused on the use of nebulized antibiotics in COPD patients. The aims of this study are: to establish whether a combination of nebulized colistin plus continuous cyclic azithromycin in severe COPD patients with chronic bronchial infection due to *Pseudomonas aeruginosa* reduces the frequency of exacerbations, and to assess the effect of this treatment on microbiological sputum isolates.

**Material and methods:** A retrospective cohort was created for the analysis of patients with severe COPD and chronic bronchial infection due to *P. aeruginosa* treated with nebulized colistin at the Respiratory Day Care Unit between 2005 and 2015. The number and characteristics of COPD exacerbations (ECOPD) before and up to two years after the introduction of nebulized colistin treatment were recorded.

**Results:** We analyzed 32 severe COPD patients who received nebulized colistin for at least three months (median 17 months [IQR 7–24]). All patients but one received combination therapy with continuous cyclic azithromycin (median 24 months [IQR 11–30]). A significant reduction in the number of ECOPD from baseline of 38.3% at two years of follow-up was observed, with a clear decrease in *P. aeruginosa* ECOPD (from 59.5% to 24.6%) and a *P. aeruginosa* eradication rate of 28% over the two-year follow-up.

**Conclusion:** In patients with severe COPD and chronic bronchial infection due to *P. aeruginosa*, combination therapy with nebulized colistin and continuous cyclic azithromycin significantly reduced the number of ECOPD, with a marked decrease in *P. aeruginosa* sputum isolates.

**Keywords:** COPD, exacerbation, azithromycin, colistin, *Pseudomonas aeruginosa*

## Introduction

In patients with severe chronic obstructive pulmonary disease (COPD), infectious exacerbations (ECOPD) are associated with poor prognosis.<sup>1,2</sup> Some interventions in this disease aim to prevent exacerbations, in order to improve the course of COPD.

*Pseudomonas aeruginosa* is responsible for 5–10% of COPD exacerbations.<sup>3</sup> Patients with severe and very severe COPD have a higher risk of suffering exacerbations due to this potentially pathogenic microorganism (PPM) than patients with mild or moderate COPD.<sup>4,5</sup> In a recent 3-year follow-up study conducted in a

Correspondence: Concepción Montón  
Department of Respiratory Medicine,  
Hospital de Sabadell, Institut Universitari  
Parc Taulí-UAB, Parc Taulí I, Sabadell,  
Barcelona 08208, Spain  
Tel +34 93 7458262  
Email cmonton@tauli.cat

cohort of severe COPD patients, *P. aeruginosa* was isolated in nearly 35%. Moreover, 12% of patients with *P. aeruginosa* isolates developed chronic bronchial colonization by this PPM, which also presented clonal persistence.<sup>6</sup> Recovery of *P. aeruginosa* has also been associated with increased mortality.<sup>3,7</sup>

Inhaled antibiotics are approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of chronic bronchial infection by *P. aeruginosa* in cystic fibrosis (CF). In these patients, Saiman et al<sup>8</sup> also demonstrated that continuous cyclic azithromycin significantly improved lung function and reduced exacerbations when added to standard therapy, which included a nebulized antibiotic in more than half of the patients. Since then, chronic antibiotic treatment with inhaled antibiotics and oral macrolides has been used to treat chronic bronchial infection by *P. aeruginosa* in CF, and the extension of these treatments to non CF-bronchiectasis has been recommended in recent guidelines.<sup>9–11</sup> The last update of the GOLD guidelines for COPD recommends the use of oral azithromycin treatment in COPD patients with frequent ECOPD despite triple inhaled therapy, and the use of nebulized antibiotics in cases with associated bronchiectasis.<sup>12</sup> However, these recommendations are mainly based on consensus; the scientific evidence is scarce and only a few small studies have focused on the use of nebulized antibiotics in COPD patients.<sup>13–15</sup>

The aim of our study is to evaluate the efficacy of combination therapy with nebulized colistin and continuous cyclic azithromycin on the frequency of exacerbations in severe COPD patients with chronic bronchial infection due to *P. aeruginosa*, when these antibiotics are added to the baseline treatment. We also aim to assess the eradicating effect of this antibiotic combination on the chronic presence of this PPM in the bronchial tree.

## Materials And Methods

### Design And Patients

A retrospective cohort was created including all patients with severe COPD and chronic bronchial infection due to *P. aeruginosa* attending the Respiratory Day Care Unit at Sabadell Hospital, Barcelona, who initiated a treatment with nebulized colistin between 2005 and 2015, in combination with long-term oral azithromycin. Patients with bronchiectasis as a main diagnosis were excluded. Chronic bronchial infection due to *P. aeruginosa* was defined as the presence of three or more positive sputum samples, collected at one-month intervals, over at least six months.<sup>9</sup>

The patients were enrolled in the cohort when starting nebulized colistin and were followed for a period of up to two years from their inclusion. Annual events occurring one year before and two years after enrolment were assessed, including the number of ECOPD and sputum cultures with isolates of PPMs, in order to evaluate the efficacy of the chronic antibiotic therapy. Only patients who had used inhaled colistin for a minimum of three consecutive months in the study period were included in the present analysis. All patients underwent the same scheduled clinical assessments at the Respiratory Day Care Unit conducted by the same team of pulmonologists before and after starting nebulized therapy.<sup>16</sup> Data were collected at each 3-month control visit while the patient was stable, and when exacerbations appeared. The study was approved by the Ethics Committee of the ParcTauli University Hospital (CEIC number 2017/555) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

### Nebulized Colistin And Continuous Cyclic Azithromycin

All patients received nebulized colistin in two possible forms of administration: 1) Generic nebulized colistin with Jet nebulizer (PARI-LC-PLUS<sup>®</sup>, PARI): 1,000,000–2,000,000 UI/12 hrs; or 2) Colistin Promixin<sup>®</sup> with I-neb adaptive aerosol delivery device (Philips Respironics): 500,000–1,000,000 UI/12 hrs. The treatment regimen was administered according to current national guidelines on bronchiectasis.<sup>9,17</sup>

The first doses were administered at the hospital for tolerance assessment, and the treatment was discontinued in patients with bronchospasm on the first administration of nebulized colistin. A forced spirometry was performed before and after the first dose of nebulized antibiotic for closer monitoring of adverse events, and any FEV<sub>1</sub> reduction of more than 200 mL and 12% was also considered as a contraindication for continuing the treatment. Continuous cyclic azithromycin (500 mg three times for week orally) was introduced at the same time as nebulized colistin, or during the previous months, in the patients enrolled.

### Definition And Treatment Of Exacerbations

ECOPD was defined as a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, of acute onset, requiring a

change in regular treatment (antibiotics with or without corticosteroids, with or without hospital admission) in a patient with underlying COPD.<sup>18</sup> ECOPD were attended from Monday to Friday (8 am to 5 pm) at the Respiratory Day Care Unit, always by the same team of pulmonologists;<sup>16</sup> outside these hours, exacerbations were attended at the emergency department. A chest radiograph was performed for each ECOPD to exclude acute pneumonia. ECOPD attended at primary care were also recorded. Antibiotics were prescribed during ECOPD according to Anthonisen's criteria<sup>19</sup> and were adjusted according to sputum culture antibiograms. Decisions regarding hospital admission were made in accordance with clinical practice guidelines.<sup>20</sup> Nebulized colistin was stopped during hospital admissions.

## Bacteriological Assessments

Sputum samples were collected from all patients for each ECOPD and during stable phases, in accordance with routine clinical practice, and were processed locally by Gram stain and bacteriological culture. All bacterial isolates were identified and antibiograms were performed following standardized microbiological protocols.<sup>21</sup> Microorganisms isolated during ECOPD were classified into four groups: Group 1, common respiratory PPMs (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and methicillin-susceptible *Staphylococcus aureus* MSSA); Group 2, methicillin-resistant *Staphylococcus aureus* (MRSA); Group 3, *Pseudomonas aeruginosa*; and Group 4, other Gram-negative bacteria (*Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Serratia marcescens*, *Escherichia coli* and *Proteus mirabilis*).

To evaluate the microbiological efficacy of the combination therapy of nebulized colistin and continuous cyclic azithromycin, eradication was defined as the absence of *P. aeruginosa* after the introduction of the treatment and during the first and second years of follow up.

Multidrug resistant *P. aeruginosa* was defined as resistance to at least one agent in three or more antibiotic groups, including beta-lactams (penicillins plus  $\beta$ -lactamase inhibitor, cephalosporins and carbapenems), quinolones, aminoglycosides, monobactam and polymyxins.<sup>22</sup>

## Statistical Analysis

Means and standard deviations (SD) or medians and interquartile ranges (IQR) were used to summarize continuous variables, as appropriate. Absolute and relative frequencies were used for categorical variables. The number of

exacerbations per year was adjusted according to the length of follow-up.

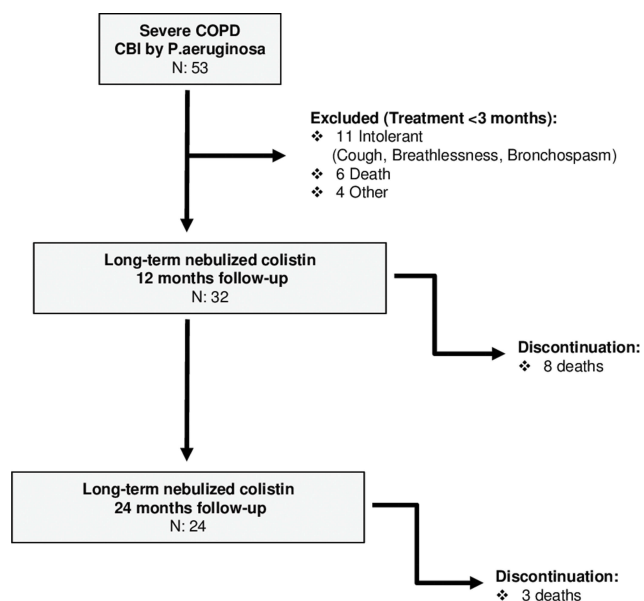
A random intercept linear mixed model for repeated measures with fixed effects of follow-up time was used to estimate the population mean of exacerbations, number of hospitalizations, and length of hospital stay at different time-points. These estimations allowed the calculation of the percentage changes over time from baseline. All statistical analyses were performed in R (The R Foundation for Statistical Computing Platform, version 3.5.0) and *lme4* package for R.

## Results

Fifty-three patients with severe COPD and chronic bronchial infection due to *P. aeruginosa* started treatment with nebulized colistin at Respiratory Care Day Unit at some point between 2005 and 2015. The main reason for discontinuation of nebulized colistin during the first three months was intolerance due to respiratory symptoms, mainly cough, breathlessness or bronchospasm, which was observed in 11 patients (20.8%). Of these patients with colistin intolerance, two presented bronchospasm at the first administration, while the remaining nine presented respiratory symptoms at home which obliged treatment withdrawal during the first three months. Ten additional patients who initiated nebulized colistin were excluded from the study due to death or other causes. Overall, 32 of the 53 patients who had initiated nebulized colistin had followed this treatment during at least three months, and were included in the study (Figure 1).

A good quality forced spirometry before and after the colistin nebulization trial (not showing significant changes) was obtained in 19 of these 32 participants (59.4%).

Baseline characteristics of the 32 participating patients are shown in Table 1. Bronchiectasis was identified in 25 patients in the computed tomography scan (78%) and most patients were treated with inhaled triple therapy (78%). The median (IQR) duration of treatment with nebulized colistin was 17 (7–24) months. Only 9% of patients (3/32) presented bronchospasm as a late adverse event (after the first 3-month period of treatment). Continuous cyclic azithromycin was used during colistin therapy by all patients but one (due to pharmacological interactions). The median duration of azithromycin therapy was 24 (IQR 11–30) months. Azithromycin was started before nebulized colistin in 17 patients (55%) and simultaneously in the remaining 14 (45%).



**Figure 1** Flow chart. Flow-chart illustrating the patients treated with nebulized colistin at Respiratory Care Day Unit during a 10-year period (2005–2015) and the patients who received nebulized colistin for at least three months and were finally included in the study.

### Respiratory Exacerbations

In the 12 months prior to the start of nebulized colistin, the 32 study participants presented a total of 126 ECOPD, with a median of four ECOPD per patient [IQR 3–5]. Eighty-five (67%) were severe enough to require hospitalization (median of three admissions per patient [IQR 1–4]), representing a total hospital stay of 1625 days (median 49 days per patient [IQR 14.5–70]). Data regarding respiratory exacerbations during the first and second years of follow-up are detailed in [Table 2](#), which shows a clear reduction in ECOPD, hospitalizations and length of hospital stay. The mixed model applied showed that combination therapy with nebulized colistin and continuous cyclic azithromycin attained an estimated mean reduction in ECOPD of 38.3% with respect to baseline after 24 months ([Figure 2](#)), and parallel reductions in hospitalizations and hospital stays of up to 41.5% and 41.9% respectively ([Figures 3 and 4](#)). The data of the fixed effects of the model applied for ECOPD, hospitalizations and days of hospital stay are detailed in [Tables 3–5](#); they reached statistical significance for ECOPD frequency, and borderline significance for hospitalizations due to respiratory disease.

### Microbiology

After nebulized colistin plus azithromycin therapy, ECOPD caused by *P. aeruginosa* decreased markedly

**Table 1** Baseline Characteristics Of COPD Patients Chronically Colonized By *P. Aeruginosa*

Characteristics (n = 32)	Results
Age(years), mean (SD)	74 (7)
Male, n (%)	32 (100)
Current smoker, n (%)	1 (3)
Pack-year, mean (SD)	60.6 (30.8)
BMI (Kg/m <sup>2</sup> ), mean (SD)	24.1 (4)
Bronchiectasis, CT scan, n (%)	25 (78)
<b>Lung function, mean (SD)</b>	
FEV1, liters	0.98 (0.4)
FEV1, % predicted	34.4 (13.7)
FVC, liters	2.5 (0.6)
FVC, % predicted	61.4 (15.6)
FEV1/FVC %	39.4 (10.7)
pO <sub>2</sub> (mmHg)	62.4 (10.4)
pCO <sub>2</sub> (mmHg)	43.8 (6.4)
BODE index	4.6 (1.6)
<b>COPD treatment, n (%)</b>	
Inhaled triple therapy (LAMA+LABA+ICs)	25 (78)
Roflumilast	1 (3)
Theophylline	2 (6)
Chronic oxygen therapy	13 (41)

**Abbreviations:** COPD, chronic obstructive pulmonary disease; SD, standard deviation; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; BMI, body mass index; BODE index, body mass index, airflow obstruction, Dyspnea and exercise capacity index; LAMA, Long-acting anti-muscarinic; LABA, long-acting β-Agonist; ICs, inhaled corticosteroids; CT, computed tomography.

during the first and second year of follow-up. ECOPD caused by common PPMs showed only small variations, with a slight decrease during the first year of follow-up and a slight increase during the second year. ECOPD caused by MRSA and other Gram-negative bacteria also showed a slight increase during the two years of follow-up ([Table 6, Figure 5](#)).

*P. aeruginosa* sputum isolates (related to the number of sputum samples obtained) clearly decreased during follow-up, not only in exacerbations but also in the regular stable phase sampling ([Figure 6](#)). Eradication of *P. aeruginosa* in the first year of follow-up was observed in 15 patients (47%), and in nine patients cultures remained negative for this PPM after two years (28%). Therefore, 6/15 (40%) patients presented a recurrence of *P. aeruginosa* isolation during the second year.

*P. aeruginosa* sputum isolates were multidrug resistant to antibiotics in 14 patients at baseline (43.7%), and this percentage did not increase throughout follow-up (11 patients, 34.3%). No resistance to colistin was observed during follow-up.

**Table 2** Respiratory Exacerbations Before And After Combination Therapy With Nebulized Colistin And Continuous Cyclic Azithromycin. For Differences Between Periods, See Table 3–5

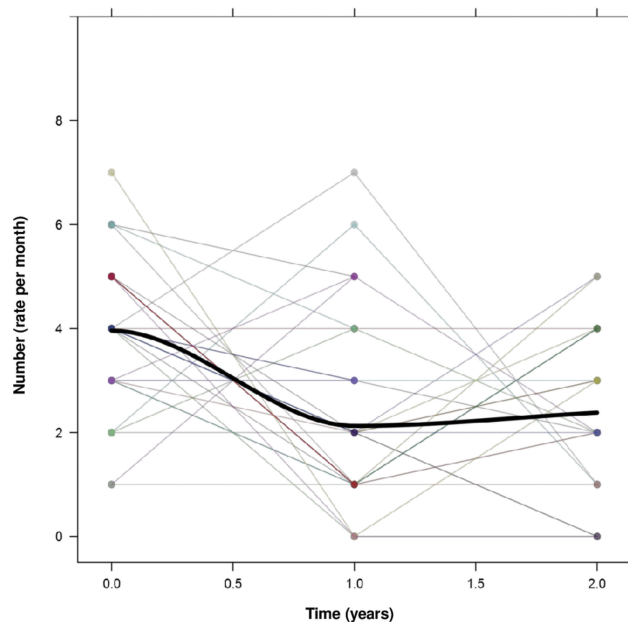
Variable	No Nebulized Colistin (Baseline)	Long-Term Nebulized Colistin Plus Azithromycin	
	Prior 12 Months (n:32)	0-12 Months (n:32)	12-24 Months (n:24)
<b>Exacerbation</b>			
- Total (n)	126	76	57
- Median per year [IQR]	4 [3-5]	2 [1-3.2]	2 [1-4]
- Median per month [IQR]	0.33 [0.25-0.42]	0.17 [0.08-0.35]	0.17 [0.14-0.33]
<b>Hospitalization</b>			
- Total (n)	85	46	35
- Median per year [IQR]	3 [1-4]	1 [0-2]	1 [0-3]
- Median per month [IQR]	0.25 [0.08-0.33]	0.08 [0-0.17]	0.08 [0-0.25]
<b>Hospital stay (days)</b>			
- Total (n)	1625	1108	595
- Median per year [IQR]	49 [14.5-70]	9 [0-49.2]	20.5 [0-45.2]
- Median per month [IQR]	0.13 [0.04-0.19]	0.05 [0-0.13]	0.06 [0-0.13]

Abbreviation: IQR, interquartile range.

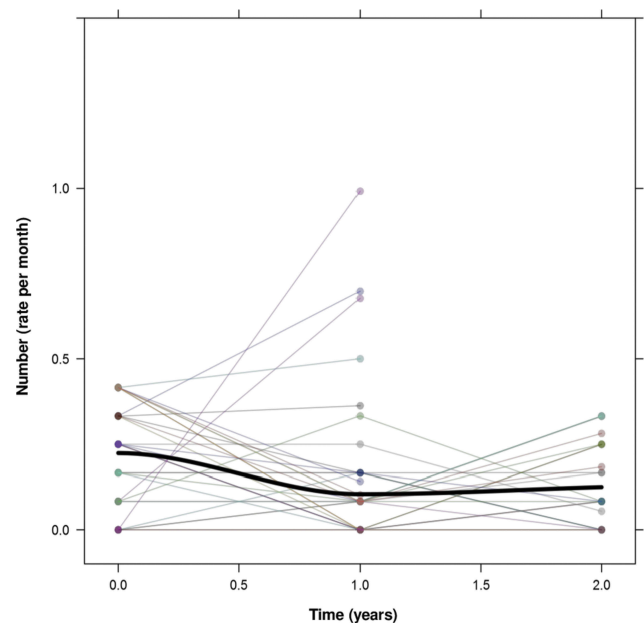
## Discussion

To our knowledge, this is the first study to examine the long-term clinical and microbiological effectiveness of the introduction of nebulized colistin in combination with continuous cyclic azithromycin for the treatment of patients with severe COPD, chronic bronchial infection

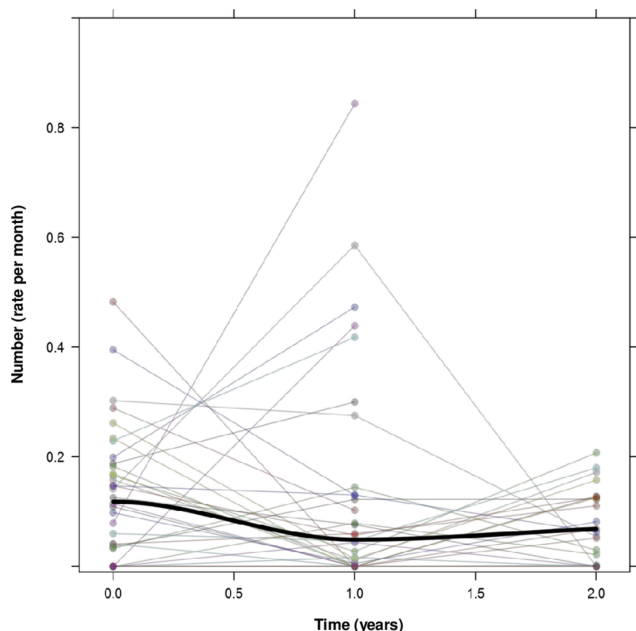
due to *P. aeruginosa* and frequent exacerbations. This combination therapy achieved a significant reduction in the number of ECOPD during the 2-year follow-up, with a marked decrease in *P. aeruginosa* sputum isolates not only in exacerbations but also in stable periods, and with good tolerance in most of the patients.



**Figure 2** Exacerbations (rate per month). Number of ECOPD per patient before (time 0) and after nebulized colistin, at first and second year. Each patient is represented by a thin unbroken coloured line. The thick black line represents the estimated average decrease in the whole group based upon the applied mixed model for repeated measures with fixed effects of follow-up time.



**Figure 3** Hospitalizations (rate per month). Number of hospitalizations due to respiratory disease per patient before (time 0) and after nebulized colistin, in the first and second years. Each patient is represented by a thin unbroken coloured line. The thick black line represents the estimated average decrease of the whole group based upon the applied mixed model for repeated measures with fixed effects of follow-up time.



**Figure 4** Days of hospital stay (rate per month). Number of days of hospital stay due to respiratory disease per patient before (time 0) and after nebulized colistin, at first and second year. Each patient is represented by a thin unbroken coloured line. The thick black line represents the estimated average decrease in the whole group based upon the applied mixed model for repeated measures with fixed effects of follow-up time.

Inhaled antibiotics are approved by the US Food and Drug administration and the European Medicines Agency for treatment of chronic bronchial infection due to *P. aeruginosa* in CF. In these patients, Saiman et al have also demonstrated that continuous cyclic azithromycin significantly improves lung function and reduces

**Table 3** Random Intercept Linear Mixed Model For Repeated Measures With Fixed Effects Of Follow-Up Time Used To Estimate The Population Mean Of ECOPD

Fixed Effects	Estimate	Standard Error	t value	p value
(Intercept)	0.3258	0.0302	10.7873	< 0.0000
Time	-0.0624	0.0250	-2.4920	0.0157

**Table 4** Random Intercept Linear Mixed Model For Repeated Measures With Fixed Effects Of Follow-Up Time Used To Estimate The Population Mean Of Hospitalizations Due To Respiratory Disease

Fixed Effects	Estimate	Standard Error	t value	p value
(Intercept)	0.2211	0.0291	7.5991	<0.0000
Time	-0.0458	0.0241	-1.9008	0.0626

**Table 5** Random Intercept Linear Mixed Model For Repeated Measures With Fixed Effects Of Follow-Up Time Used To Estimate The Population Mean Of Days Of Hospital Stay Due To Respiratory Disease

Fixed Effects	Estimate	Standard Error	t value	p value
(Intercept)	0.1484	0.0241	6.1633	<0.0000
Time	-0.0311	0.0197	-1.5770	0.1205

exacerbations.<sup>8</sup> Treatment with inhaled antibiotics and oral macrolides has been extended to chronic bronchial infection by *P. aeruginosa* in non CF-bronchiectasis, and has been included in different guidelines as a consensus recommendation,<sup>9-11</sup> in spite of the limited evidence available in non-CF patients.

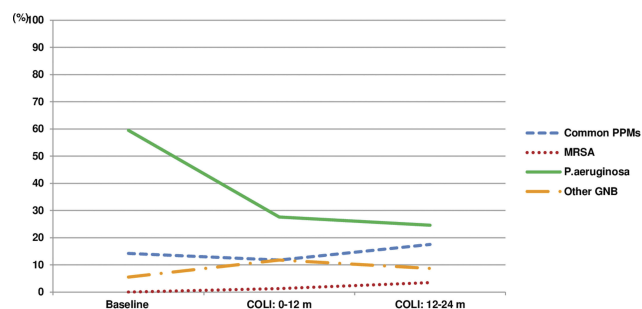
Although it is well known that *P. aeruginosa* frequently causes exacerbations in severe COPD, which evolves to chronic bronchial colonization in over 10% of patients,<sup>6</sup> so far the experience with inhaled antibiotics in COPD patients is very limited. Steinfors et al<sup>15</sup> included four severe COPD in a group of 18 patients with chronic respiratory disease (non-CF bronchiectasis) and chronically infected by Gram-negative bacteria, who were treated with nebulized colistin for at least six months. These authors reported a slower decline in lung function with this treatment and an improvement in quality of life. Later, Dal Negro et al<sup>13</sup> used nebulized tobramycin for 14 days in 13 patients with severe COPD colonized by multiresistant *P. aeruginosa*, finding a short-term reduction in local inflammation and a long-term reduction in bacterial load and severe exacerbations during a 6-month follow-up. More recently, Bruguera-Avila et al<sup>14</sup> reported a prospective study of 36 COPD patients with chronic or intermittent bronchial colonization by *P. aeruginosa* treated with long-term nebulized colistin (at least three months of treatment and 1-year follow-up), in which they found reductions in the number and length of admissions after treatment initiation. Similarly, our data confirmed a decrease in the number of hospitalizations due to ECOPD in severe COPD patients colonized by *P. aeruginosa*, and demonstrated an additional effect on moderate exacerbations, with a significant reduction in the total number of ECOPD over the two years of treatment. This reduction, previously suggested in studies with a shorter follow-up,<sup>13,14</sup> highlights the long-term beneficial effect of inhaled colistin in this clinical setting, when added to oral macrolides.

**Table 6** Number Of Microbiological Isolates And Percentages Adjusted Per Total Number Of ECOPD Before And After Combination Therapy With Nebulized Colistin And Continuous Cyclic Azithromycin

Microbiological Isolates Number (%ECOPD)	No Nebulized Colistin	Long-Term Nebulized Colistin Plus Azithromycin	
	Number Of Isolates Prior 12 Months (n:32) ECOPD n:126	Number Of Isolates 0-12 Months (n:32) ECOPD n: 76	Number Of Isolates 12-24 Months (n:24) ECOPD n: 57
<b>Group 1:</b> <b>Common potentially pathogenic microorganisms</b>			
<i>H.influenzae</i>	18 (14.2)	9 (11.8)	10 (17.5)
<i>S. pneumoniae</i>	4 (3.2)	1 (1.3)	1 (1.7)
<i>S. pneumoniae</i>	5 (3.4)	5 (6.6)	7 (12.3)
<i>M. catarrhalis</i>	9 (7.1)	2 (2.6)	0 (0)
MSSA	0 (0)	1 (1.3)	2 (3.5)
<b>Group 2:</b> <b>MRSA</b>	0 (0)	1 (1.3)	2 (3.5)
<b>Group 3:</b> <b><i>Paeruginosa</i></b>	75 (59.5)	21 (27.6)	14 (24.6)
<b>Group 4:</b> <b>Other Gram-negative bacteria</b>			
<i>S.maltophilia</i>	7 (5.5)	9 (11.8)	5 (8.7)
<i>S.maltophilia</i>	1 (0.7)	0 (0)	3 (5.2)
<i>A.xylosoxidans</i>	6 (4.7)	8 (10.5)	1 (1.7)
<i>S.marcescens</i>	0 (0)	0 (0)	0 (0)
<i>E. coli</i>	0 (0)	1 (1.3)	1 (1.7)
<i>P. mirabilis</i>	0 (0)	0 (0)	0 (0)

**Abbreviation:** ECOPD, chronic obstructive pulmonary disease exacerbation.

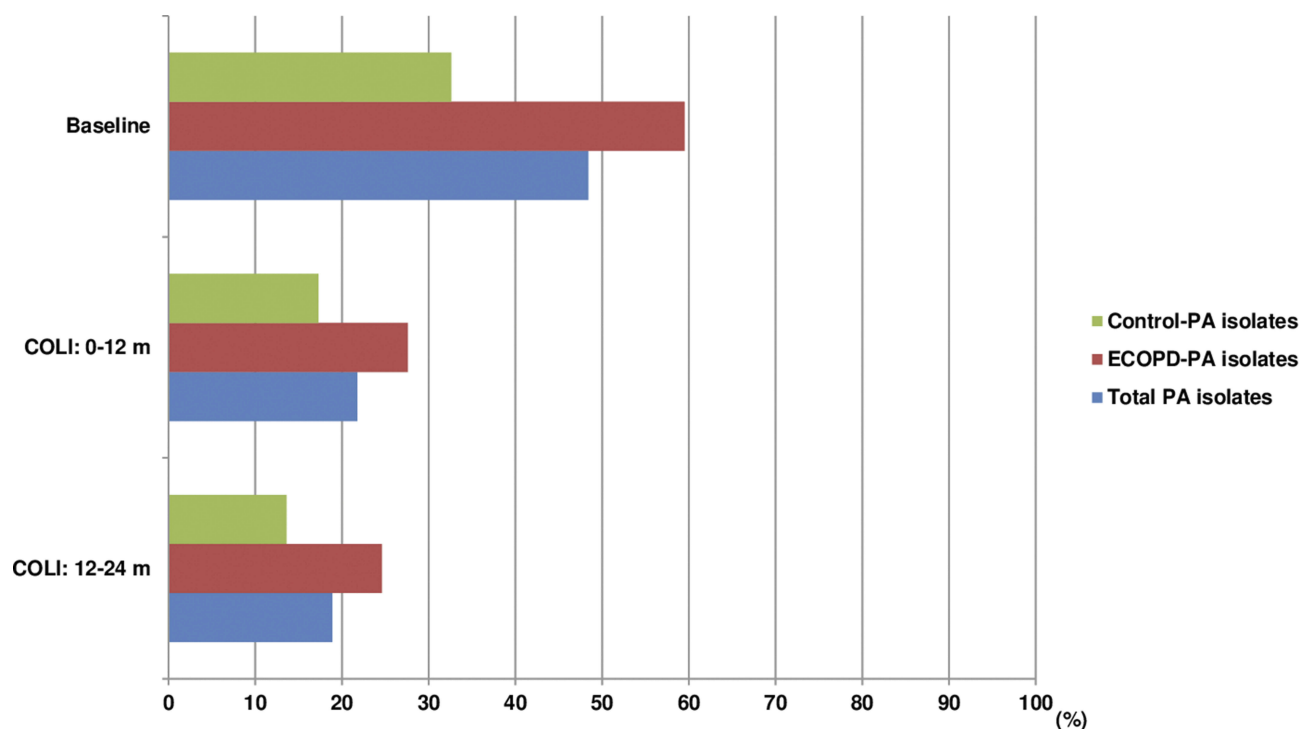
The beneficial effects of macrolides in COPD patients are mediated by the inhibition of quorum sensing and biofilm formation, mechanisms which have been proven particularly useful in reducing the virulence of *P. aeruginosa* and in facilitating the activity of antipseudomonal antibiotics.<sup>23</sup> In a previous study conducted by our group<sup>24</sup> to evaluate the usefulness of long-term cyclic



**Figure 5** Long-term nebulized colistin and ECOPD microbiology. ECOPD microbiology in the 12 months prior to starting nebulized colistin (baseline) with respect to the first and second year afterwards. *Common PPMs*, common potential pathogenic microorganisms; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa* and *Other GNB*, other Gram-negative bacteria; COLI, nebulized colistin.

azithromycin therapy in reducing exacerbation frequency, a small subgroup of patients with chronic *P. aeruginosa* colonization also treated with nebulized colistin was included, and presented a statistically significant reduction in ECOPD of 43%. These preliminary results suggest that the combination of long-term cyclic azithromycin therapy and nebulized antibiotics may be useful in this group of patients. Our group has previously confirmed that continuous cyclic azithromycin therapy as a single antimicrobial therapy, for more than one year, reduces the number of ECOPD due to common PPMs, albeit associated with a relative increase in ECOPD due to *P. aeruginosa*.<sup>25</sup> Therefore, considering that patients treated with long-term cyclic azithromycin are susceptible to developing chronic bronchial infection by *P. aeruginosa*, the addition of nebulized antibiotics active against this PPM seems justifiable.

The fall in exacerbations in COPD patients colonized by *P. aeruginosa* in our study is paralleled by a marked decrease in *P. aeruginosa* sputum isolates, not only in exacerbations but also in stable phase. This may be considered as the main



**Figure 6** *P. aeruginosa* sputum isolates before and after nebulized colistin. *P. aeruginosa* sputum isolates (related to the number of sputum samples obtained) in the 12 months prior to starting nebulized colistin (baseline) with respect to the first and second year afterwards. COLI, nebulized colistin; Total PA-isolates, Total *P. aeruginosa* isolates in exacerbations and in stable phase; ECOPD PA-isolates, *P. aeruginosa* isolates in exacerbations; Control PA-isolates, *P. aeruginosa* isolates in stable phase.

explanation of the fall in the number of ECOPD, while the number of ECOPD due to other microorganisms did not change significantly. These microbiological effects have not been reported in previous studies conducted in severe COPD patients,<sup>14</sup> but are particularly relevant for the identification of the mechanisms underlying the observed improvement in the evolution of severe COPD patients when using the combined therapy. On this issue, we can only say that our eradication rate of *P. aeruginosa* at 1-year follow-up is slightly higher than that observed by Bruguera-Avila et al<sup>14</sup> (47% versus 39%), probably due to the addition of cyclic azithromycin to the treatment and its indirect antimicrobial effects.

Although nebulized colistin was generally well tolerated in our study, adverse events such as bronchospasm were more frequent than in previous reports. Episodes of bronchospasm were not reported by Dal Negro et al<sup>13</sup> and accounted for only 11% in the study conducted by Bruguera-Avila et al.<sup>14</sup> However, the differences between these publications may be related to differences in study design, which means that comparison is difficult. The results of the present study point to the need for careful monitoring of COPD patients when initiating inhaled colistin, previous to their maintenance on long-term inhaled therapy.

This study has several limitations: its retrospective design, the limited sample size (with only men included), and the absence of a control group (either untreated or treated only with azithromycin). However, among its strengths are the fact that it reflects the situation in real life and describes practices that are now recommended in clinical guidelines but are not backed as yet up by a large body of evidence.

In conclusion, this study shows that the use of nebulized colistin added to continuous cyclic azithromycin as a combination therapy in severe COPD patients with chronic bronchial infection by *P. aeruginosa* achieves a significant reduction in the number of ECOPD over a 2-year period, with a marked decrease in *P. aeruginosa* sputum isolates, not only in exacerbations but also in the stable phase, and relatively good tolerance. Further studies with prospective designs and with a larger number of patients are now needed to elucidate the role of each chronic antibiotic treatment (inhaled antibiotics and oral macrolides) and their interactions. These studies should also help to establish the most appropriate treatments for severe COPD patients with chronic bronchial infection by *P. aeruginosa*, and the timings of their introduction – a particularly important issue, given that this situation is often difficult to handle in clinical practice.



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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

None of the authors have any conflict of interests to declare regarding this manuscript.

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