


# Eradication of *Pseudomonas aeruginosa* with inhaled colistin in adults with non-cystic fibrosis bronchiectasis

Chronic Respiratory Disease  
Volume 16: 1–9  
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DOI: 10.1177/1479973119872513  
journals.sagepub.com/home/crd  


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## Abstract

The persistent isolation of *Pseudomonas aeruginosa* in the airways of non-cystic fibrosis bronchiectasis (NCFB) patients is associated with a worsening of the symptoms, increase of exacerbations, poor quality of life and functional impairment. The objective of this study was the analysis of the eradication rate of *P. aeruginosa* in the sputum of patients with NCFB treated with inhaled colistin and the effects of the treatment in the exacerbations. This was a prospective, cohort, study of 67 NCFB patients treated with inhaled colistin at the Hospital of A Coruña (Spain). We recorded dyspnoea, exacerbations, lung function and sputum cultures of *P. aeruginosa* in the patients. The mean age of the patients was  $67.25 \pm 14.6$  years (59.7% male). The percentages of eradication of *P. aeruginosa* in sputum at 3, 6, 9 and 12 months were 61.2%, 50.7%, 43.3% and 40.3%, respectively. We observed a significant decrease in exacerbations after 1 year of colistin treatment ( $1.98 \pm 3.62$ ) versus the previous year ( $3.40 \pm 4.21$ ,  $p < 0.001$ ). We conclude that treatment with inhaled colistin in patients with NCFB and *P. aeruginosa* in sputum can achieve high rates of eradication even in patients with several previous positive cultures, as well as a significant decrease of exacerbations and hospital admissions.

## Keywords

Bronchiectasis, *Pseudomonas aeruginosa*, inhaled antibiotics, colistin, eradication

Date received: 25 January 2018; accepted: 2 August 2019

## Introduction

In recent years, there has been an increase in the prevalence of non-cystic fibrosis bronchiectasis (NCFB)<sup>1</sup> and in the economic burden caused by its management.<sup>2</sup> Chronic bronchial infection (CBI) is frequently associated with NCFB and characteristically the dominant pathogens are *Pseudomonas aeruginosa* and *Haemophilus influenzae*.<sup>3,4</sup> Infection with *P. aeruginosa* is associated with worsening of symptoms,<sup>5</sup> poorer health-related quality of life,<sup>6</sup> increased exacerbations and accelerated decline in forced respiratory volume in the first second (FEV<sub>1</sub>).<sup>7,8</sup> Also, it is one of the predictive factors of worse prognosis in the available severity indexes.<sup>7,9</sup>

Eradication of *P. aeruginosa* in CBI is challenging due to its ability to growth in biofilms, the fast appearance of resistant strains, and the difficulty of reaching adequate concentrations of antibiotics in the bronchial space with conventional treatments in

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some cases.<sup>10–14</sup> However, successful eradication is usually high in young (68–93%) and adult (79%) cystic fibrosis (CF) patients using a variety of antipseudomonal regimens, with an average time of reappearance of 8–18 months.<sup>15–19</sup>

There are few studies of the possible role of inhaled antibiotics in the treatment of NCFB, and they are highly heterogeneous.<sup>13,15,20–23</sup> Two studies with tobramycin were prospective trials with a placebo control group, but with a reduced number of patients.<sup>13,23</sup> The few studies with inhaled colistin did not exceed 30 patients each and in only one of them systemic antibiotics had been used previously.<sup>15,21,22</sup>

Despite the limited data available, the clinical guidelines recommend the use of inhaled antibiotics for the treatment of early infection by *P. aeruginosa*.<sup>24,25</sup> In contrast to CF, for which the prescription of simultaneous systemic and inhaled antibiotics is recommended,<sup>6,26</sup> for NCFB inhaled antibiotic (tobramycin or colistin for 3–12 months) is recommended only after failure of a previous eradicating attempt with oral ciprofloxacin and/or an intravenous (IV) cycle with two antipseudomonal antibiotics.<sup>24,25</sup>

The primary aim of this study was to evaluate the efficacy of an antibiotic eradication protocol for *P. aeruginosa* infection consisting of the administration of systemic antibiotics followed by inhaled colistin for 12 months in a cohort of patients with NCFB. The secondary aim was to determine whether the use of inhaled colistin is associated with decreased exacerbations with respect to the year prior to the initiation of treatment.

## Material and methods

This 12-month prospective study was conducted between 1 January 2010 and 31 August 2015 at the bronchiectasis outpatient clinic of the University Hospital in A Coruña (Spain). The research protocol described here adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Review Board of the Hospital Universitario A Coruña. All patients were informed orally and in writing of the procedures, potential risks and implications of accepting this study.

This study included consecutive NCFB patients aged  $\geq 18$  years if they had (1) a diagnosis based on clinical presentation and high-resolution computed tomography (HRCT), (2)  $\geq 1$  cultures of *P. aeruginosa* but had not previously had eradication therapy, (3) treatment with inhaled colistin and follow-up for at least 1 year from the

start of the inhaled antibiotic, and (4) no modifications in the base treatment for respiratory disease during the study period including previous year.

The exclusion criteria were (1) patients with CF or traction bronchiectasis due to pulmonary fibrosis, (2) indication of inhaled colistin as lung transplant prophylaxis, (3) infection with other Gram-negative non-fermenter bacteria, (4) having started treatment with regular nebulized antibiotics without prior IV or oral antipseudomonal antibiotics, (5) patients that achieved successful eradication of *P. aeruginosa* with only systemic antibiotic treatment, and (6) lack of compliance with follow-up protocol.

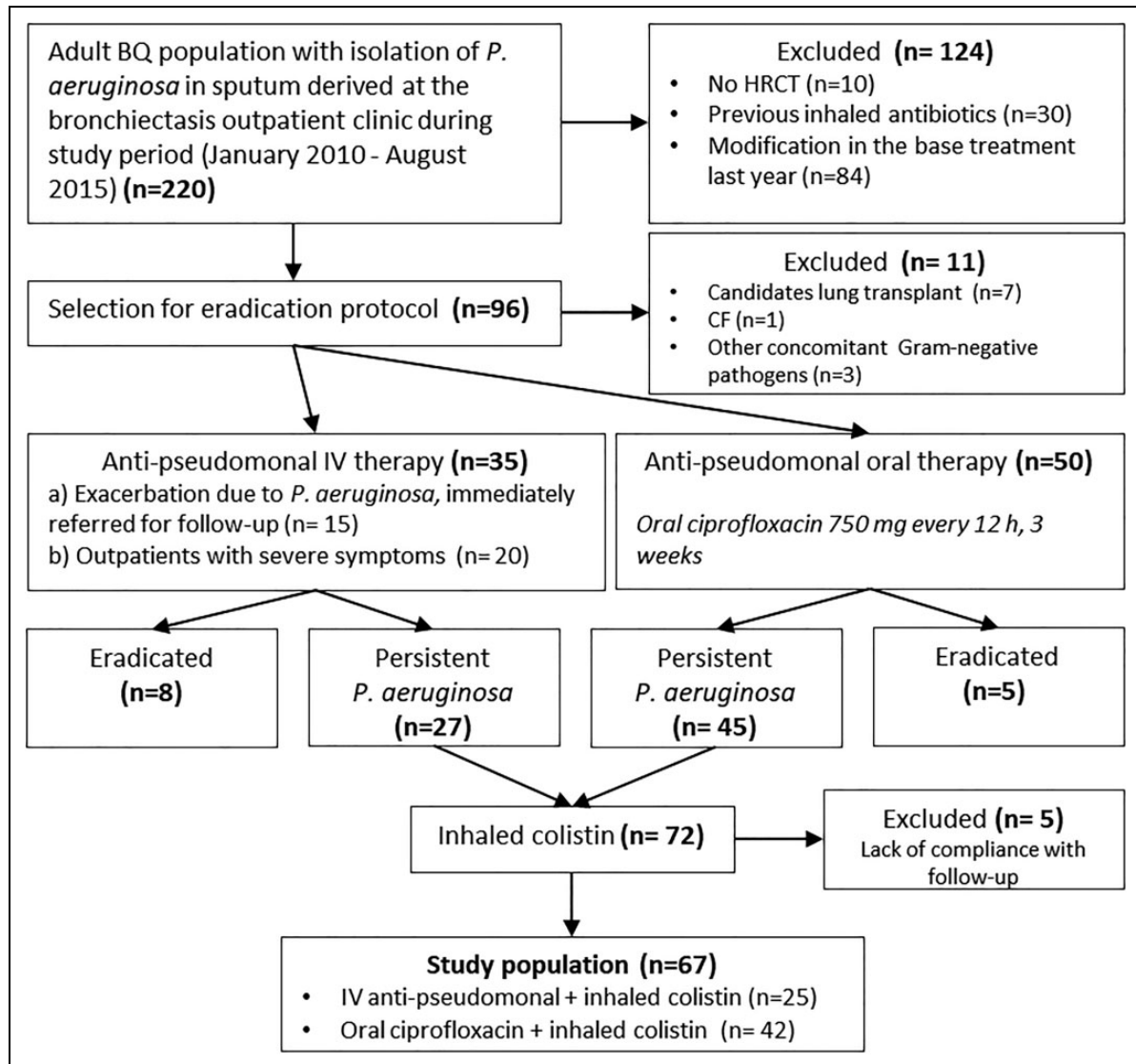
Patients underwent standard clinical follow-up procedures and all of them were informed about the collection of data from their medical history, and gave informed consent.

## Study design

In the first assessment (inclusion visit), all patients underwent the same diagnostic protocol as suggested by the 2010 British Thoracic Society and Spanish guidelines.<sup>24,25</sup> We routinely attempt to diagnose the aetiology of bronchiectasis following established guidelines.<sup>24</sup>

We collected data on demographics, exposure factors, familiar genetic diseases, co-morbidities, long-term treatments, respiratory symptoms (cough, sputum, dyspnoea using the Medical Research Council scale), physical exploration, microbiological findings in sputum cultures in previous year, HRCT, laboratory determinations including immunoglobulins (IgG, IgA, IgM, IgE), alfa-1 antitrypsin, autoimmunity, sweat test for chloride concentration (genetic testing in case of suspected CF) and number of exacerbations in previous year (oral cycles of antibiotics, emergency visits or hospitalizations). Clinical, radiological and treatment histories were obtained from the electronic health records and from the interview to the patient. Spirometry was performed in all patients, including forced vital capacity (FVC) and FEV<sub>1</sub>.<sup>27</sup>

All patients with positive culture for *P. aeruginosa* received an eradication protocol which included oral ciprofloxacin 750 mg twice daily for 3 weeks (mild-moderate symptoms in outpatients) or IV tobramycin 5 mg/kg plus beta-lactam antipseudomonal antibiotics for 2 weeks (outpatients with severe symptoms, with purulent bronchorrhea, or patients admitted for exacerbation due to *P. aeruginosa* that were immediately referred for follow-up). Variations from the



**Figure 1.** Chart showing participants in the study. BQ: bronchiectasis; HRCT: high-resolution computed tomography; CF: cystic fibrosis; IV: intravenous; OR: oral.

protocol occurred mainly because of drug allergy, intolerance or insusceptibility, and in this case two alternative IV antipseudomonal antibiotics were used at the clinician's discretion. In case of persistence of *P. aeruginosa* in the sputum, inhaled colistin (Promixin 1 MIU twice daily) was administered with the I-neb<sup>®</sup> Adaptive Aerosol Delivery (AAD) device (Philips Respironics, Chichester, UK) during a 12-month period (Figure 1). Subjects were instructed to self-administer the treatment at home. A short-acting bronchodilator was administered before nebulized colistin as needed in case of cough and/or wheezing in order to reduce adverse effects.

Monitoring of the patients followed standard clinical practice in visits every 3 months. Subjects were

questioned concerning adherence to the treatment, changes in symptoms such as cough, dyspnoea, sputum production and wheezing. Blood tests (serum chemistry, haematology) and spirometry were performed in each visit. Samples of sputum were cultured monthly during the first 3 months and every 2 months thereafter.

All bacteriological analyses were performed on spontaneous sputum samples obtained before colistin administration and tested the presence of *P. aeruginosa* and other typical respiratory pathogens. The Murray–Washington criteria for sputum quality were used in all cases, with all samples having less than 10 squamous cells and more than 25 leukocytes per low-power microscope field. All samples were

cultured in standard blood agar and Mc-Conkey and Saboraud media. The microorganisms isolated were identified by standardized or automated means, and the antibiogram was made.

Eradication of *P. aeruginosa* was defined as a negative culture on all sputum samples taken at the moment of evaluation (3, 6, 9 and 12 months since the beginning of treatment). Inhaled colistin was stopped only in the case of negative cultures of *P. aeruginosa* for at least 12 months. CBI was defined by the isolation of *P. aeruginosa* in sputum culture on three or more occasions, at least 1 month apart. Patients who were unable to provide sputum samples due to the absence of a productive cough were classified as not having chronic infection for the purposes of analysis. In case of CBI, inhaled colistin treatment was continued indefinitely.

The number of episodes of exacerbations was recorded for 1 year pre- and post-eradication protocol. An exacerbation of bronchiectasis was defined as a clinical deterioration for which oral or IV antibiotics were prescribed in the presence of at least one (and usually more than one) of the following symptoms: increasing cough, increasing sputum volume, worsening sputum purulence, worsening dyspnoea, increased fatigue/malaise, fever and haemoptysis. Exacerbations were classified as ambulatory management, emergency visits or hospital admission. Exacerbations were recorded from patient histories and verified using administrative databases. Previous exacerbations were defined with the same criteria as for the prospectively recorded exacerbations during colistin treatment.

### Statistical analysis

We initially performed a descriptive analysis of the variables included in the study. The qualitative variables are presented as absolute values and percentages. For quantitative variables, the results are expressed as means and standard deviations, maximum and minimum values and quartiles.

Univariate comparisons between patients with or without eradication in the 3-, 6-, 9- and 12-month periods were tested with Pearson's  $\chi^2$  or Fisher's exact test for categorical variables. We used the Wilcoxon test to compare continuous variables after analysing the normality assumption with the Kolmogorov–Smirnov test. Variables selected for comparison between groups (eradication vs. non-eradication at different times) were age, gender (female vs. male),

smoking status (never smoked vs. ex/active smoker), first positive sputum cultures of *P. aeruginosa*, proportion of patients with concomitant azithromycin treatment, systemic antibiotics used for eradication (oral ciprofloxacin vs. IV antipseudomonal antibiotics), *P. aeruginosa* morphotype mucoid, mean FVC post-bronchodilatation (% predicted) and FEV<sub>1</sub> post-bronchodilatation (% predicted). A logistic regression analysis was performed to determine the factors related to the eradication of *P. aeruginosa*. Age and gender were included as covariates in all models, as well as all variables with  $p < 0.10$  in univariate analysis (concomitant treatment with azithromycin, *P. aeruginosa* mucoid) and also included variables that showed significant influence in literature in eradication in CF (first positive sputum for *P. aeruginosa* and systemic antibiotics). A forward stepwise strategy was used. Statistical analysis was performed using the SPSS software package version 20.0 (SPSS Inc., USA). A  $p$  value  $< 0.05$  was considered statistically significant for all analyses.

### Results

Ninety-six patients diagnosed with NCFB and presenting *P. aeruginosa* in sputum were selected for the eradication protocol. Eleven patients were excluded due to the following reasons: seven patients had indication related to infection prophylaxis for lung transplantation, one was diagnosed with CF during the follow-up, three had other concomitant Gram-negative microorganism different from *P. aeruginosa* when treatment started. Of the remaining 85 patients, 13 achieved successful eradication with only systemic antibiotic treatment, and 5 failed to comply with first follow-up visit. The data correspond to 67 patients with a mean age of  $67.25 \pm 14.6$  years (range 16–87 years), predominantly males (59.7%). Patient baseline characteristics are shown in Table 1. Twenty-five patients received 2 weeks of IV antipseudomonal antibiotics and the remaining 42 patients received oral ciprofloxacin.

Table 2 shows the number of positive *P. aeruginosa* sputum cultures per patient prior to the administration of inhaled colistin. Nineteen patients (28.3%) started treatment after two sputum cultures positive for *P. aeruginosa* (one isolate prior to the systemic antibiotic regimen and persistence in control sputum), and in 48 patients (72%) *P. aeruginosa* had been isolated on three or more occasions.

**Table 1.** Patient characteristics at the beginning of treatment ( $n = 67$ ).

Age (years), mean $\pm$ SD (range)	67.25 $\pm$ 14.6 (16–87)
Sex, % males	59.7
Tobacco use, $n$ (%)	
Ex-smokers	26 (39)
Smokers	4 (6)
Cause of bronchiectasis, $n$ (%)	
COPD	26 (38.8)
Post-infective	10 (14.9)
Unknown	9 (13.4)
Asthma	8 (11.9)
Immune defect	5 (7.5)
Deficit of alfa-1 antitrypsin	4 (6.0)
Rheumatoid arthritis	2 (3.0)
Ciliary dyskinesia	2 (3.0)
Yellow nail syndrome	1 (1.5)
Coinfection with other pathogens, $n$ (%)	
<i>Staphylococcus aureus</i>	2 (3.0)
<i>Haemophilus influenzae</i>	6 (10.0)
<i>Streptococcus pneumoniae</i>	4 (6.0)
<i>Pseudomonas aeruginosa</i> infection, $n$ (%)	
First-ever isolation	19 (28.3)
Previously isolated	48 (71.7)
Inhaled corticosteroids, $n$ (%)	55 (87)
Bronchodilators, $n$ (%)	60 (95)
Macrolides, $n$ (%)	46 (69)
Dyspnoea MRC, $n$ (%)	
Grade 0	6 (9)
Grade 1	15 (22.4)
Grade 2	29 (43.3)
Grade 3	15 (22.4)
Grade 4	2 (3)
Dyspnoea MRC, media $\pm$ SD	1.88 $\pm$ 0.96
Cystic BQ (HRCT), $n$ (%)	15 (23)
Mean FVC post-bronchodilatation, L $\pm$ SD	2.64 $\pm$ 0.88
Mean FVC post-bronchodilatation, % predicted $\pm$ SD	79.62 $\pm$ 20.50
Mean FEV1 post-bronchodilatation, L $\pm$ SD	1.44 $\pm$ 0.67
Mean FEV1 post-bronchodilatation, % predicted $\pm$ SD	57.49 $\pm$ 24.74
FEV1/FVC, ratio $\pm$ SD	54.59 $\pm$ 14.66
Mean exacerbations in the previous year, mean $\pm$ SD	3.40 $\pm$ 4.21
0	10 (14.9)
1	10 (14.9)
2	14 (20.9)
$\geq 3$	33 (49)

$n$  = number of patients; SD: standard deviation; COPD = chronic obstructive pulmonary disease; MRC = dyspnoea according to the Medical Research Council scale; BQ = bronchiectasis; HRCT = high-resolution computed tomography; FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 second.

**Table 2.** Number of positive sputum for *P. aeruginosa* (separated at least 1 month) previous to the initiation of the treatment with systemic antibiotics followed by inhaled colistin.<sup>a</sup>

Number	Frequency	Percentage
2	19	28.3
3	13	19.4
4	13	19.4
5	8	12.0
6	2	3.0
7	1	1.5
8	1	1.5
9	2	3.0
$\geq 10$	8	12.0

<sup>a</sup>All patients had at least two positive sputum previous to the start of the treatment with inhaled colistin because of the two previous attempts at eradication with antibiotics.

The eradication of *P. aeruginosa* after 3 months was observed in 41 patients (61.2%), of whom 34 patients (50.7%) continued with negative cultures after 6 months, 29 patients (43.3%) after 9 months and 27 patients (40.3%) after 1 year. There were eight patients (11.9%) presenting positive cultures at month 3 of the treatment who were negative at month 6. Of these, seven patients (10.7%) remained negative after 9 and 12 months.

We did not observe significant differences in the eradication of *P. aeruginosa* in the short or long term depending on the number of previous positive sputum cultures (2 or  $\geq 3$ ) (Table 3). Differences in other variables between patients with and without eradication at 3, 6, 9 and 12 months are shown in Table 4. In the logistic regression model, the only variable associated to the eradication rate was the presence of the mucoid *P. aeruginosa* ( $p < 0.001$ ).

We observed a decrease in the number of exacerbations after administration of inhaled colistin from (mean  $\pm$  SD) 3.40  $\pm$  4.21 in the year before to 1.98  $\pm$  3.62 the following year ( $p < 0.001$ ). When the type of exacerbations (oral antibiotic cycles, emergency visits or hospital admissions) were analysed independently, a significant reduction in both hospital admissions ( $p < 0.001$ ) and number of antibiotic cycles ( $p = 0.018$ ) was also observed, but not of emergency visits ( $p = 0.526$ ) (Table 5). Most patients (70%) had two or more exacerbations in the previous year. Of the 19 patients who had the first hospital admission in the previous year, 4 patients (21%) had at least one admission the following year.

**Table 3.** Eradication of *P. aeruginosa* after 3, 6, 9 and 12 months as a function of number of previous positive sputum.

	Eradication				<i>p</i> Value <sup>a</sup>
	Yes		No		
	<i>n</i>	%	<i>n</i>	%	
Eradication at month 3					0.785
2 sputum, <i>n</i> = 19	11	58	8	42	
≥3 sputum, <i>n</i> = 48	30	62	18	38	
Eradication at month 6					0.531
2 sputum, <i>n</i> = 19	10	53	9	47	
≥3 sputum, <i>n</i> = 48	24	50	24	50	
Eradication at month 9					0.438
2 sputum, <i>n</i> = 19	9	47	10	53	
≥3 sputum, <i>n</i> = 48	20	42	28	58	
Eradication at month 12					0.319
2 sputum, <i>n</i> = 19	9	47	10	53	
≥3 sputum, <i>n</i> = 48	18	38	30	62	

<sup>a</sup> $\chi^2$  test.

Mild adverse effects (cough and/or wheezing) were reported by five (7.5%) patients during the first month of treatment but did not result in discontinuation of therapy.

## Discussion

This study shows that *P. aeruginosa* may be eradicated in a high percentage of NCFB patients with a treatment based on systemic antibiotics followed by inhaled colistin even when previously they had presented several positive cultures. In addition, our study suggests that this therapy may be effective in reducing exacerbations. In our study, we observed eradication rates of *P. aeruginosa* in NCFB patients of 61.2, 50.7, 43.3 and 40.3% after 3, 6, 9 and 12 months of treatment, respectively.

There are only three published studies that analyse the use of inhaled colistin for *P. aeruginosa* eradication in NCFB patients. Two studies including 18 and 19 patients found that eradication success was lower than ours (21.4% and 16%, respectively) after an average 41 and 21.2 months of treatment.<sup>21,22</sup> The possible reasons for these differences with our study are that in these cases the patients had not received systemic antibiotics previous to inhaled colistin, a different colistin regimen and type of nebulizer, or no treatment with macrolides. In our study, 69% of the patients maintained a simultaneous treatment with macrolides.

A prospective study with 25 patients receiving inhaled colistin plus systemic antibiotics for 3 months showed an eradication rate of 43% at 14.3 months, very similar to ours at 12 months.<sup>15</sup> Although the value of systemic antibiotics in *P. aeruginosa* eradication therapy in NCFB patients is still under investigation, the results of White et al. and our study coincide in presenting higher eradication rates than studies that use inhaled antibiotic only. The use of oral/IV antibiotics may increase the chances of eradication because inhaled antibiotics may not reach areas of the lung due to obstruction of the airways by mucus.

The largest study to date with inhaled colistin included 144 patients (73 treated with colistin, 71 with placebo) and was carried out over 6 months with a dose of 1 MIU every 12 hours.<sup>12</sup> Although a significant decrease in the load of *P. aeruginosa* was reported, the efficacy of eradication was not specified.

Two studies using only inhaled tobramycin have shown eradication rates of 35% and 22.2% at 6 and 12 weeks, respectively.<sup>13,20</sup> The only randomized, placebo-controlled study using IV ceftazidime plus tobramycin during 14 days followed by inhaled tobramycin for 3 months reported an eradication rate of 54.5% after 15 months, in line with our results.<sup>23</sup> The success of the eradication therapy in this last case can be due to having started after a first isolate of *P. aeruginosa* from sputum in contrast with typically after the second or more isolates. However, in our study, we did not obtain significant differences in the eradication rate as a function of the number of previous positive sputum with *P. aeruginosa*, suggesting that eradication should be attempted both when *P. aeruginosa* isolation is recent as if there is long-term chronic infection.

Currently the optimal treatment regimen and duration has not been determined. The studies of White and Orriols reached eradication rates similar to ours after 3 months but in the first case the treatment also included oral ciprofloxacin and in the second the treatment was started after first isolation and did not include patients with mucoid *P. aeruginosa*.<sup>15,23</sup> Compared with non-mucoid *P. aeruginosa*, the mucoid morphotype is associated with a lower percentage of success in eradication treatment.<sup>28,29</sup> In our study, up to 72% of the patients had more than three *P. aeruginosa*-positive sputum isolations and in 59.7% of these the morphotypes were mucoid. Our results differ from some authors that suggest that the timing of the administration of antimicrobial therapy may be critical, as there may be a window of

**Table 4.** Characteristics of patients with NCFB with and without *P. aeruginosa* eradication in the 3, 6, 9 and 12 months follow-up.<sup>a,b</sup>

Eradication	3 months		6 months		9 months		12 months	
	Yes (n = 41)	No (n = 26)	Yes (n = 34)	No (n = 33)	Yes (n = 29)	No (n = 38)	Yes (n = 27)	No (n = 40)
Age (years)	65.9 ± 14.8	69.3 ± 14.0	64.5 ± 15.6	70.1 ± 13.0	63.7 ± 16.3	69.9 ± 12.6	64.4 ± 16.4	69.1 ± 13.1
Sex, males, n (%)	24 (58.5)	16 (61.5)	19 (55.9)	21 (63.6)	16 (55.2)	24 (63.2)	15 (55.6)	25 (62.5)
Ex/active smokers, n (%)	19 (46.3)	11 (42.3)	15 (44.1)	15 (45.5)	12 (41.4)	18 (47.4)	11 (40.7)	19 (47.5)
First <i>P. aeruginosa</i> culture, n (%)	11 (26.8)	8 (30.7)	10 (29.6)	9 (27.3)	9 (31.0)	10 (26.3)	9 (33.3)	10 (25.0)
Concomitant azithromycin, n (%)	27 (65.9)	19 (73.1)	23 (67.6)	23 (69.7)	18 (62.1)	28 (73.7) <sup>c</sup>	16 (59.3)	30 (75)
Oral ciprofloxacin	26 (63.4)	16 (61.5)	22 (64.7)	20 (60.6)	19 (65.5)	23 (60.5)	17 (63.0)	25 (62.5)
<i>P. aeruginosa</i> mucoid	18 (43.9)	22 (84.6) <sup>d</sup>	14 (41.2)	26 (78.8) <sup>c</sup>	10 (65.5)	30 (78.9) <sup>d</sup>	8 (70.4)	32 (80) <sup>d</sup>
Mean FVC post-BD, % predicted	80.4 ± 21.5	78.3 ± 19.2	80.2 ± 23.1	79.1 ± 17.9	80.3 ± 20.8	79.1 ± 20.4	80.1 ± 21.2	79.3 ± 20.2
Mean FEV <sub>1</sub> post-BD, % predicted	58.3 ± 26.3	56.1 ± 22.5	57.5 ± 27.1	57.4 ± 22.7	57.6 ± 26.7	57.3 ± 23.4	56.7 ± 27.4	58.1 ± 23.1

NCFB: non-cystic fibrosis bronchiectasis; FVC post-BD: forced vital capacity post-bronchodilatation (% predicted); FEV<sub>1</sub> post-BD: forced expiratory volume in 1 second post-bronchodilatation (% predicted).

<sup>a</sup>Data are presented as mean ± standard deviation (X ± SD).

<sup>b</sup>p Values: comparisons between groups were tested using the Pearson's  $\chi^2$  (categorical variables) or Wilcoxon test (non-normally distributed continuous variables after analysing the normality with Kolmogorov–Smirnov test).

<sup>c</sup>p < 0.1.

<sup>d</sup>p < 0.001.

**Table 5.** Number of exacerbations before and during treatment with inhaled colistin.

	n	Mean ± SD	Difference	p Value <sup>a</sup>
Hospital admissions				<0.001
Previous year	75	1.14 ± 1.56	0.712	
During treatment	28	0.42 ± 1.33		
Emergency room visits				0.526
Previous year	18	0.28 ± 0.89	−0.077	
During treatment	23	0.35 ± 1.36		
Cycles of antibiotics				0.018
Previous year	128	1.94 ± 2.80	0.758	
During treatment	78	1.18 ± 1.73		
Total exacerbations				<0.001
Previous year	214	3.40 ± 4.21	1.381	
During treatment	129	1.98 ± 3.62		

n = number of patients; SD = standard deviation.

<sup>a</sup>Test of Wilcoxon.

opportunity after which antibiotic eradication treatment is no longer successful. In our study, 10% of the patients reached eradication after the third month. Our current practice is to maintain inhaled antibiotic for 1 year after the last positive isolation.

Sodium colistimethate is usually used at a dose of 2 million IU every 12 hours dissolved in 4 ml of the most isotonic solution possible, but with the use of the I-neb nebulizer (Philips Respironics®) the dose can be reduced to 1 million IU every 12 hours. The medication is released only during patient inhalation and not continuously as in all other nebulizers.

Comparison of exacerbations between pre- and post-treatment with inhaled colistin found a significant reduction in the number of exacerbations during the year with treatment. We observed significantly reduced hospital admissions and antibiotic cycles in the patients treated, but not of visits to the emergency room (ER). This reflects the fact that exacerbations that require a visit to the ER are usually severe and result in hospital admission. There are a few small studies that have demonstrated a significant reduction in exacerbations in line with our study.<sup>11,14,22</sup> Besides, in one of the most important clinical trials of aerosolized antibiotics for patients with NCFB, a clear trend of increase of time to first exacerbation was demonstrated when patients with good adherence to treatment were selected.<sup>12</sup> Our results are consistent with a recent study that showed that an important risk factor predicting benefit from inhaled antibiotics is a history of frequent pulmonary exacerbations.<sup>30</sup> In our case, 70% of the patients had >2 exacerbations in the previous year, while 40% of the patients in the clinical trial had no exacerbations in the previous year. A strength of our study is that the number of exacerbations is quite high in a large number of patients; in contrast, several recent trials have failed due to a low exacerbation rate in the patients.

The main limitations of our study were that it was performed in a single centre with no placebo-controlled group. However, our methods and management by a

single researcher assured low variability in data acquisition and homogeneous management of patients and application of clinical protocols before and after the intervention. Other possible limitation is that, although we verified the collection of the drug at the Pharmacy and also evaluated self-reported adherence in a structured interview in each visit, we did not perform an analysis of the stored adherence data in the I-neb nebulizer system. However, all patients attended all follow-up visits. Finally, another possible limitation of the study was that the patient selection was not homogeneous with regard to timing of *P. aeruginosa* infection. However, this fact has allowed us to observe that eradication is possible even in patients with several previous isolations.

We conclude that a high rate of long-term eradication of *P. aeruginosa* in NCFB patients can be achieved with administration of systemic antibiotics followed by inhaled colistin, and we recommend this approach based on our experience with patients in real clinical conditions. *Pseudomonas* eradication should be attempted even when *Pseudomonas* is present in several samples of sputum. In line with previous studies of different aerosolized antibiotics for NCFB,<sup>11,12,14,22</sup> our study demonstrated a notable clinical impact of inhaled colistin, with a significant reduction of exacerbations and an ensuing significant decrease in hospital admissions.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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