Inhaled Colistin in Patients with Bronchiectasis and Chronic *Pseudomonas aeruginosa* Infection

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Abstract

Rationale: Chronic infection with *Pseudomonas aeruginosa* is associated with an increased exacerbation frequency, a more rapid decline in lung function, and increased mortality in patients with bronchiectasis.

Objectives: To perform a randomized placebo-controlled study assessing the efficacy and safety of inhaled colistin in patients with bronchiectasis and chronic *P. aeruginosa* infection.

Methods: Patients with bronchiectasis and chronic *P. aeruginosa* infection were enrolled within 21 days of completing a course of antipseudomonal antibiotics for an exacerbation. Participants were randomized to receive colistin (1 million IU; n = 73) or placebo (0.45% saline; n = 71) via the I-neb twice a day, for up to 6 months.

Measurements and Main Results: The primary endpoint was time to exacerbation. Secondary endpoints included time to exacerbation based on adherence recorded by the I-neb, *P. aeruginosa* bacterial density, quality of life, and safety parameters. All analyses were on the intention-to-treat population. Median time (25% quartile) to exacerbation was 165 (42) versus 111 (52) days in the colistin and placebo groups, respectively ($P = 0.11$). In adherent patients (adherence quartiles 2–4), the median time to exacerbation was 168 (65) versus 103 (37) days in the colistin and placebo groups, respectively ($P = 0.038$). *P. aeruginosa* density was reduced after 4 ($P = 0.001$) and 12 weeks ($P = 0.008$) and the St. George's Respiratory

Questionnaire total score was improved after 26 weeks ($P = 0.006$) in the colistin versus placebo patients, respectively. There were no safety concerns.

Conclusions: Although the primary endpoint was not reached, this study shows that inhaled colistin is a safe and effective treatment in adherent patients with bronchiectasis and chronic *P. aeruginosa* infection.

Clinical trial registered with <http://www.isrctn.org/> (ISRCTN49790596)

Keywords: randomized controlled trial; nebulized antibiotics; adherence

At a Glance Commentary

Scientific Knowledge on the Subject: Chronic infection with *Pseudomonas aeruginosa* affects 12–27% of adults with bronchiectasis and is associated with increased exacerbation frequency and poor clinical outcomes. The evidence base supporting the use of nebulized antibiotics in these patients is weak.

What This Study Adds to the Field: This randomized controlled study shows improved clinical and patient-reported outcomes with colistin administered through the I-neb adaptive aerosol delivery device in adherent patients with bronchiectasis and chronic *P. aeruginosa* infection.

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Individuals with bronchiectasis present with symptoms of persistent or recurrent bronchial sepsis related to irreversibly damaged and dilated bronchi (1). Recent data showing a direct relationship between bacterial load, airway inflammation, and risk of exacerbation are consistent with the “vicious cycle hypothesis” of bronchiectasis (2, 3) and support the rationale for antibiotic prophylaxis (4).

Chronic infection with *Pseudomonas aeruginosa* affects 12–27% of adults with bronchiectasis (5–10) and is associated with an increased exacerbation frequency (8), an accelerated rate of FEV₁ decline (7), more extensive bronchiectasis on computed tomography (11), and increased mortality (12). Because of the worse clinical outcomes associated with chronic infection with *P. aeruginosa*, the British Thoracic Society guidelines on bronchiectasis recommend the prescription of nebulized antibiotics in such patients if they have a high infection frequency (1). However, the evidence base for this recommendation is weak. Studies evaluating nebulized tobramycin demonstrated excellent microbiologic outcomes, but the formulations tested were poorly tolerated (13–15). A subsequent study of nebulized gentamicin in patients with predominantly *Haemophilus influenzae* (46%) or *P. aeruginosa* (42%) reported better tolerability and marked improvements in bacterial load, exacerbation frequency, exercise tolerance, and patient-reported outcomes (16). Recent phase II studies of inhaled ciprofloxacin have shown encouraging results including marked reductions in *P. aeruginosa* bacterial density (17, 18), but an international phase III study of nebulized aztreonam conducted in similar patients failed to meet its efficacy endpoints and was associated with a high incidence of adverse events (AEs) (19).

Nebulized colistin is commonly prescribed for patients with bronchiectasis in Europe (20), but has not been evaluated in a clinical study setting to date. We performed a randomized, double-blind, placebo-controlled study of nebulized colistin administered through the I-neb adaptive aerosol delivery device (Philips Respironics, Chichester, UK) in patients with bronchiectasis and chronic *P. aeruginosa* infection. The I-neb is a unique device that monitors the time and peak flow of the first three breaths during nebulization and then pulses aerosol at the start of the inspiratory

phase to optimize drug delivery (21). Nebulization is silent, it takes approximately 3 minutes, and the device informs the patient when the dose has been delivered. It also provides a precise record of nebulizer use through an electronic download.

Some of the results of this study have been previously reported in the form of abstracts (22–24).

Methods

The study was conducted at 35 centers in the United Kingdom, Russia, and Ukraine. Participants were 18 years of age or older, had bronchiectasis confirmed by computed tomography, had two or more positive respiratory tract cultures for *P. aeruginosa* in the preceding 12 months, and were

Figure 1. Flow diagram of patients enrolled in a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of up to 6 months of therapy with inhaled colistin in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection. *Treatment difference in incidence of treatment-emergent adverse events leading to discontinuation ($P = 0.56$). †Patient (placebo) was withdrawn from the study after one dose of investigation medicinal product because she did not meet the entry criteria ($>15\%$ fall in FEV₁ within 30 min of the first dose). AE = adverse event; ITT = intention-to-treat.

within 21 days of completing a course of antipseudomonal antibiotics for the treatment of an exacerbation. *P. aeruginosa* also had to be cultured from a sputum sample taken at the screening visit.

Participants provided written informed consent. The study was approved by the central Independent Ethics Committee for each country.

Participants were randomly allocated (1:1) to colistin, 1 million international units, in 1-ml 0.45% saline or placebo (1 ml 0.45% saline). The investigator and study participants were masked to treatment allocation.

The first dose was administered under supervision and patients with 15% or more reduction in FEV₁ within 30 minutes of nebulization were withdrawn. Those that remained in the study administered the study drug twice a day for 6 months or until they developed an exacerbation.

Exacerbations were defined as the presence of three or more of the following signs or symptoms for at least 24 hours: increased cough, increased sputum volume, increased sputum purulence, hemoptysis, increased dyspnea, increased wheezing, fever ($\geq 38^{\circ}\text{C}$) or malaise, and the treating physician agreed that antibiotic therapy was required.

Study visits were scheduled at Weeks 4, 12, and 26, or earlier if the patient developed an exacerbation. At study visits, patients completed the St. George's Respiratory Questionnaire (SGRQ) (25) (Week 12, Week 26, or exacerbation visits), submitted a sputum sample for quantitative culture and susceptibility testing, submitted a 24-hour sputum collection (baseline and Week 4 visits), performed spirometry, and reported AEs. In addition, adherence data were downloaded from the I-neb.

The primary endpoint was the time to exacerbation. The secondary efficacy endpoints were time to exacerbation based on adherence recorded by the I-neb, severity of exacerbation, CFUs of *P. aeruginosa*, 24-hour sputum weight, and SGRQ total score. Secondary safety endpoints included bronchoconstriction in the 30 minutes post first dose of study drug, FEV₁, sensitivity of *P. aeruginosa* to colistin, CFUs of other potentially pathogenic microorganisms, and AE reporting.

Statistical Analysis

To have 80% power to detect a 75% difference in median time to exacerbation,

Table 1: Baseline Characteristics of Patients

	Colistin Group (n = 73)	Placebo Group (n = 71)
Sex, n (%)		
Male	27 (37%)	34 (48%)
Female	46 (63%)	37 (52%)
Age, yr, mean (SD)	58.3 (15.3)	60.3 (15.8)
FEV ₁ , L, mean (SD)	1.55 (0.89)	1.56 (0.65)
Predicted FEV ₁ , %, mean (SD)	55.9 (24.3)	57.6 (24.9)
Weight of sputum collected over 24 h (g) before baseline visit, mean (SD)	28.0 (25.9)	28.6 (20.1)
Azithromycin therapy, n (%)	6 (8%)	5 (7%)
Prior inhaled antibiotic therapy	0	0

67 patients per treatment group were required. The calculation assumed a two-sided significance test performed at the 5% level, a median time to exacerbation of 60 days in the placebo group (16), and study duration of 6 months per patient. To allow for dropouts, 7.5% more patients were recruited to the study (n = 144).

All analyses were performed on the intention-to-treat (ITT) population using SAS statistical software, release 9.1.3 (SAS Corporation, Cary, NC). A Kaplan-Meier survival curve of time to exacerbation was plotted for each treatment group and the median time to exacerbation was estimated using survival analysis. The log-rank test was used to compare the treatment groups and the analysis was stratified by center. Time to exacerbation in relation to adherence recorded by the I-neb was summarized in quartiles based on percentage adherence and treatment differences were analyzed as per the primary endpoint.

Additional information on the study methods is available in the online supplement.

Results

A total of 230 patients were screened for eligibility and 144 patients were randomized (Figure 1); all participants received at least one dose of the assigned study drug (colistin, n = 73; placebo, n = 71) and were included in the ITT analyses. Eleven patients in each group did not complete the study. Table 1 shows the baseline characteristics; there were no between-group differences for any parameter. Adherence data recorded by the I-neb are summarized in Table 2.

Primary Endpoint: Time to First Exacerbation

A total of 36 of 73 (49%) patients in the colistin group experienced an exacerbation

Table 2: Adherence with Study Medication

	Colistin Group (n = 73)	Placebo Group (n = 71)
Level of adherence, n (%) [*]		
<60%	4 (5.7)	7 (10.0)
60 to <70%	6 (8.6)	4 (5.7)
70 to <80%	6 (8.6)	5 (7.1)
80 to <90%	11 (15.7)	15 (21.4)
$\geq 90\%$	43 (61.4)	39 (55.7)
Mean (SD)	87.3 (15.4)	85.0 (18.4)
Median (range)	92.7 (27.5–109.3)	91.7 (25.0–117.4)
25% quartile	82.4	80.8
75% quartile	97.0	97.5
Not recorded	3	1

^{*}For patients with recorded data, n = 70 (colistin) and n = 70 (placebo).

Figure 2. Kaplan-Meier plot of estimate of time to first exacerbation within (A) the whole intention-to-treat population, and (B) adherence quartiles 2–4 of the intention-to-treat population.

compared with 42 of 71 (59%) in the placebo group; a Kaplan-Meier plot of the estimate of the time to exacerbation is depicted in Figure 2A. The median time (25% quartile) to exacerbation was 165 days (42 d) in the colistin group and 111 days (52 d) in the placebo group ($P = 0.11$).

Secondary Efficacy Endpoints

Time to first exacerbation based on adherence. To examine the effects of adherence on efficacy, the time to exacerbation was summarized in quartiles based on percentage adherence. Treatment comparisons showed a statistically significant result in favor of the active

treatment in the second adherence quartile (81–92.1%; $n = 34$; $P = 0.017$). At this level of adherence, 6 of 17 (35%) patients in the colistin group experienced an exacerbation compared with 14 of 17 (82%) in the placebo group. It was not possible to determine a median time to exacerbation in the colistin group because of the number of patients completing 6 months of therapy; in the placebo group it was 89 days. The respective 25% quartiles for time to exacerbation were 26 and 22 days. Within the first quartile (adherence <81%; $n = 34$), third quartile (adherence 92.1–97.1%; $n = 36$), and fourth quartile (adherence >97.1%; $n = 36$) there was no evidence of a treatment group difference.

Data from quartiles 2–4 were combined (adherence $\geq 81\%$). At this level of adherence, 27 of 54 (50%) patients in the colistin group experienced an exacerbation compared with 37 of 52 (71%) in the placebo group; a Kaplan-Meier plot of the estimate of the time to exacerbation is depicted in Figure 2B. The median time (25% quartile) to exacerbation was 168 days (65 d) in the colistin group and 103 days (37 d) in the placebo group ($P = 0.038$).

A *post hoc* analysis was performed in patients with greater than or equal to 80% adherence, a cut-off used to distinguish adherent from nonadherent patients (17, 26, 27). At this level of adherence, 27 of 54 (50%) patients in the colistin group experienced an exacerbation compared with 39 of 54 (72%) in the placebo group. The median time (25% quartile) to exacerbation was 168 days (65 d) in the colistin group and 103 days (37 d) in the placebo group ($P = 0.028$).

CFUs of *P. aeruginosa*. In the whole ITT population, inhaled colistin resulted in significant reductions in *P. aeruginosa* bacterial density after 4 and 12 weeks treatment compared with placebo (-1.7 [2.2] vs. -0.3 [1.9] $\log_{10}$ CFU/g, $P = 0.001$, at 4 wk; -1.6 [2.2] vs. -0.5 [2.3] $\log_{10}$ CFU/g, $P = 0.008$, at 12 wk) (Figure 3).

SGRQ total score. In the whole ITT population, colistin-treated patients experienced a mean (SD) change in SGRQ total score from baseline to Week 12 and Week 26 of -2.8 (14.5) and -10.4 (19.6) units, respectively. The corresponding results for the placebo group were -2.2 (10.5) and -0.4 (13.2) units, respectively. The estimated mean treatment differences in change in SGRQ total score from baseline to Week 12 and Week 26 were -1.09 (95% confidence interval [CI], -5.18 to 2.99) and -10.51 (95% CI, -17.87 to -3.14), respectively. This treatment difference reached statistical significance at Week 26 ($P = 0.006$) (Figure 4).

Weight of sputum. In the whole ITT population, the mean (SD) change in 24-hour sputum weight from baseline to Week 4 was -3.6 g (22.4) in the colistin group compared with -1.6 g (9.9) in the placebo group. The estimated mean treatment difference was -1.9 (95% CI, -8.3 to 4.5 ; $P = 0.56$).

Severity of exacerbations. In the whole ITT population, most exacerbations (75%

Figure 3. Change from baseline in log₁₀ CFUs *Pseudomonas aeruginosa* within the whole intention-to-treat population. The treatment difference in change from baseline in *P. aeruginosa* CFUs was analyzed using the Wilcoxon rank sum test. Error bars denote SEM.

and 79% in the colistin and placebo groups, respectively) were treated with oral antibiotics.

Secondary Safety Endpoints

Bronchoconstriction after the first dose of study drug. One patient in the placebo

group experienced a reduction in FEV₁ of greater than or equal to 15% within 30 minutes of the first dose and discontinued treatment. However, five (7%) patients in the colistin group subsequently developed bronchoconstriction that led to discontinuation of treatment.

FEV₁. In the colistin group, mean (SD) changes from baseline to Weeks 4, 12, and

26 in FEV₁ (L) were −0.03 (0.40), 0.01 (0.43), and −0.10 (0.45), respectively. The corresponding results for the placebo group were 0.02 (0.18), −0.09 (0.34), and 0.00 (0.26), respectively. The estimated mean treatment differences in change in FEV₁ (L) from baseline to Weeks 4, 12, and 26 were −0.05 (95% CI, −0.17 to 0.07), 0.11 (95% CI, −0.17 to 0.07), and −0.10 (95% CI, −0.22 to 0.02), respectively. These treatment differences did not reach statistical significance.

Microbiology. No colistin-resistant strains of *P. aeruginosa* were identified during the study (Table 3). There were no significant differences in treatment-emergent pathogens between treatment groups (Table 4).

AEs. AEs are summarized in Table 5. A total of 143 AEs were reported in 47 patients (64%) in the colistin group and 108 AEs in 38 patients (54%) in the placebo group ($P = 0.25$). No suspected unexpected serious adverse reactions were reported. There were three deaths, which were all considered unlikely related to study drug by the investigator. One death (preferred term: cardiopulmonary failure) occurred in the colistin group and two deaths (preferred terms: bronchiectasis and respiratory failure in one patient and acute coronary syndrome in one patient) occurred in the placebo group.

Discussion

Colistin administered through the I-neb increases time to exacerbation compared with placebo in adherent patients with bronchiectasis and chronic *P. aeruginosa* infection.

Use of the I-neb allowed a detailed analysis of the relationship between adherence to study drug and treatment outcome, and had a major impact on the interpretation of the results. The study failed to meet its primary endpoint of time to exacerbation within the whole ITT population because of the greater number of exacerbations experienced by poorly adherent patients assigned colistin (8 of 16 [50%]) compared with placebo (5 of 18 [28%]). When patients in adherence quartile 1 were excluded from the analysis (adherence <81%), there was a statistically significant and clinically meaningful treatment difference of 65 days in time

Figure 4. Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score within the whole intention-to-treat population. An analysis of covariance with treatment and center included in the model was used to examine treatment differences between groups for SGRQ total score. Error bars denote SEM.

Table 3: Distribution of MIC of Colistin for *Pseudomonas aeruginosa*

	Colistin Group				Placebo Group			
	N	MIC ₅₀	MIC ₉₀	MIC Range	N	MIC ₅₀	MIC ₉₀	MIC Range
Baseline	73	0.25	1.5	0.032–2.0	70	0.5	2.0	0.047–2.0
1 mo	44	0.38	1.5	0.064–2.0	49	0.5	2.0	0.064–3.0
Final visit	47	0.25	1.5	0.047–3.0	53	0.38	1.5	0.047–2.0

Definition of abbreviations: MIC = minimum inhibitory concentration; MIC₅₀ = minimum inhibitory concentration required to inhibit the growth of 50% of isolates; MIC₉₀ = minimum inhibitory concentration required to inhibit the growth of 90% of isolates; N = number of patient sputum samples with *P. aeruginosa*.

MIC in milligrams per liter.

Breakpoint MICs for colistin: susceptible ≤4; resistant >4.

Data from European Committee on Antimicrobial Susceptibility testing, last updated February 1, 2013.

to exacerbation between the colistin and placebo groups. Near identical results were found in patients with greater than or equal to 80% adherence, a cut-off used to distinguish adherent from nonadherent patients (17, 26, 27), indicating that individuals need to be adherent to gain clinical benefit from nebulized colistin. More impressive increases in time to exacerbation were reported with inhaled gentamicin and azithromycin, but these studies involved patients with bronchiectasis with lower rates of *P. aeruginosa* infection (12–42% of participants) (16, 28, 29). However, a remarkably similar treatment difference of 76 days was found between the active and placebo groups in the recent phase II study evaluating the effect of nebulized liposomal ciprofloxacin in 42 patients

with bronchiectasis and *P. aeruginosa* infection (18).

In the whole ITT population analysis, there was a significant reduction in *P. aeruginosa* density after 4 and 12 weeks of treatment with colistin compared with placebo. Although the magnitude of change was modest compared with the 4 log₁₀ reduction reported after a month of liposomal ciprofloxacin (18), it is likely the CFU change with colistin was affected by the prescription of exacerbation antipseudomonal antibiotics that triggered entry to the study. This novel study design was implemented to provide a uniform starting point for the primary endpoint of time to first exacerbation.

In the whole ITT population analysis, there was a significant improvement in SGRQ total score following 26 weeks

treatment with nebulized colistin compared with placebo. A reduction in SGRQ total score of 4 units is clinically significant (30), thus the 10.5-unit reduction seen with nebulized colistin strongly suggests it had a meaningful impact on quality of life. This finding is consistent with the SGRQ outcomes reported with nebulized gentamicin (16) and with one of the three recently published macrolide studies in which a reduction of 6.1 units was observed per 6 months of treatment compared with a 2.1-unit reduction in the placebo group (29). Because exacerbation frequency is known to have a negative impact on quality of life in patients with bronchiectasis (31, 32), the reduction in exacerbation frequency with long-term antibiotic therapy may explain the improvement in SGRQ total score in these studies.

There were no safety concerns related to the use of nebulized colistin. The incidence of AEs leading to discontinuation was extremely low and similar between treatment groups. There were no concerns with respect to renal toxicity or neuropathy. The low rate of bronchospasm related to colistin on initial testing and throughout the study is reassuring. There was no significant change in FEV₁, which is consistent with other recent studies of inhaled antibiotics in bronchiectasis (16–18). There was no evidence that use of nebulized colistin for up to 6 months led to the development of colistin-resistant isolates of *P. aeruginosa* or overgrowth of other bacteria. This is in

Table 4: Number (Percentage) of Patients with Additional Microorganisms

Microorganism	Colistin Group			Placebo Group		
	Baseline	1 Mo	Final Visit	Baseline	1 Mo	Final visit
<i>Achromobacter xylosoxidans</i>	1 (1.4%)	1 (1.8%)	0	2 (2.8%)	1 (2.0%)	1 (1.6%)
<i>Acinetobacter</i> spp.	0	0	0	2 (2.8%)	0	0
<i>Aeromonas</i> sp.	0	0	0	0	1 (2.0%)	0
<i>Aspergillus</i> spp.	2 (2.8%)	0	5 (7.5%)	4 (5.7%)	2 (3.9%)	3 (4.8%)
<i>Candida</i> spp.	2 (2.8%)	1 (1.8%)	2 (3.0%)	4 (5.7%)	1 (2.0%)	3 (4.8%)
Coliform	1 (1.4%)	0	0	0	0	1 (1.6%)
<i>Haemophilus influenzae</i>	0	0	0	1 (1.4%)	1 (2.0%)	3 (4.8%)
<i>Klebsiella pneumoniae</i>	0	0	0	1 (1.4%)	0	0
<i>Moraxella catarrhalis</i>	3 (4.2%)	0	2 (3.0%)	2 (2.9%)	1 (2.0%)	4 (6.5%)
<i>Providencia rettgeri</i>	0	0	1 (1.5%)	0	0	0
<i>Serratia marcescens</i>	0	0	0	0	0	1 (1.6%)
<i>Staphylococcus aureus</i>	3 (4.2%)	3 (5.5%)	5 (7.5%)	5 (7.1%)	8 (15.7%)	2 (3.2%)
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	1 (1.6%)
<i>Streptococcus pneumoniae</i>	2 (2.8%)	1 (1.8%)	2 (3.0%)	0	1 (2.0%)	1 (1.6%)
Number of patient samples	71	55	67	70	51	62

Limit of detection: 2×10^3 organisms per milliliter sputum for bacteria and 200 organisms per milliliter sputum for fungi.

Table 5: Summary of Adverse Events (Safety Population)

	Colistin Group (n = 73)	Placebo Group (n = 71)
Number of patients reporting TEAEs		
Any TEAEs, n (%)	47 (64.4)	38 (53.5)
Deaths, n (%)	1 (1.4)	2 (2.8)
SAEs, n (%)	6 (8.2)	4 (5.6)
AE leading to withdrawal, n (%)	7 (9.6)	6 (8.5)
Severe AEs, n (%)	7 (9.6)	3 (4.2)
Related AEs, n (%)	18 (24.7)	9 (12.7)
Total number of TEAEs reported	143	108
By severity, events (%)		
Mild	92 (64.3)	67 (62.0)
Moderate	41 (28.7)	37 (34.3)
Severe	10 (7.0)	4 (3.7)
Serious, events (%)	9 (6.3)	6 (5.6)
SUSARs	0	0
Relationship to study treatment, events (%)		
Unlikely	108 (75.5)	88 (81.5)
Possible	31 (21.7)	11 (10.2)
Probable	3 (2.1)	9 (8.3)
Definite	1 (0.7)	0
Action taken with study drug, events (%)		
None	129 (90.2)	97 (89.8)
Interrupted	4 (2.8)	2 (1.9)
Discontinued	10 (7.0)	9 (8.3)
IMP-related TEAE leading to discontinuation, events (%)	8 (5.6)	6 (5.6)
Statistical analysis of TEAEs, SAEs, and SUSARs		
Treatment difference in overall incidence of TEAEs*	P = 0.25	
Treatment difference in incidence of TEAEs leading to discontinuation*	P = 1.00	
Treatment difference in overall incidence of study drug-related TEAEs leading to discontinuation*	P = 0.75	

Definition of abbreviations: AE = adverse event; IMP = investigational medicinal product; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; TEAE = treatment-related adverse event.

*Chi-square test with continuity correction.

contrast to the 28% increase in the proportion of macrolide-resistant commensal oropharyngeal streptococci

reported after 12 months of erythromycin (33) and a macrolide resistance rate of 88% following 12 months of azithromycin

(29) in patients with bronchiectasis. *Aspergillus* species were isolated from 2.8% of sputum samples at baseline and 7.5% at the final visit of colistin-treated patients. Although similar rates of *Aspergillus* species isolation were seen in the placebo group, *Aspergillus* species are isolated more frequently following the prescription of inhaled antipseudomonal antibiotics in patients with cystic fibrosis (34).

In summary, colistin administered through the I-neb adaptive aerosol delivery device is associated with improvements in *P. aeruginosa* bacterial density, time to exacerbation, and quality of life in adherent patients with bronchiectasis and chronic *P. aeruginosa* infection. ■

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