Journal of *Respiration*

MDPI

Article

Bronchiectasis Evaluation of Adjunctive Therapy with Erdosteine and Nebulized Amikacin for Chronic Cough and Healthcare Outcomes (BEAT-COUGH Study): A Two-Centre Experience

Patil Shital [1,*], Rajesh Patil [2] and Gajanan Gondhali [2]

[1] Pulmonary Medicine, Venkatesh Chest Hospital and Critical Care Center, Latur 413512, Maharashtra, India
[2] Internal Medicine, Maharashtra Institute of Medical Sciences and Research (MIMSR) Medical College, Latur 413531, Maharashtra, India; drrspat@gmail.com (R.P.); gajanan_2226@yahoo.co.in (G.G.)
* Correspondence: drsvpatil1980@gmail.com

Abstract

Background: Chronic cough is a major determinant of impaired quality of life and recurrent exacerbations in bronchiectasis. The BEAT-COUGH Study evaluated the effectiveness of adjunctive oral erdosteine plus nebulized amikacin during acute exacerbation and long-term maintenance in patients with non-cystic fibrosis bronchiectasis. **Methods:** The BEAT-COUGH Study was a prospective, two-center observational study (VCC:37/2023) with a 52-week follow-up. A total of 164 adults with HRCT-confirmed bronchiectasis, a Modified Reiff Score > 10, acute exacerbation, and positive sputum microbiology were enrolled. Eighty-two patients received standard care alone, and 82 received standard care plus oral erdosteine and nebulized amikacin (250 mg twice daily during exacerbation, followed by once daily during maintenance). A total of 144 patients completed maintenance follow-up. Cough severity was assessed using a 100 mm Visual Analog Scale (VAS), with VAS < 20 mm defining a satisfactory response. Secondary outcomes included exacerbation frequency, duration, time to first exacerbation, exacerbation-free days, sputum rheology, microbiology, hospitalization, antibiotic use, and healthcare costs. **Results:** Adjunctive therapy produced significantly higher satisfactory cough responses during both acute exacerbation and maintenance (both $p < 0.001$). Combination therapy reduced the duration of mild, moderate, and severe exacerbations by 39.97%, 37.30%, and 30.26%, respectively (all $p < 0.0001$); prolonged time to first exacerbation and exacerbation-free days (all $p < 0.0001$); and reduced moderate and severe exacerbations while increasing the proportion of exacerbation-free patients ($p = 0.00019$). Significant improvements were observed in sputum viscosity and clearance (90.3% vs. 19.4%), sputum volume (94.4% vs. 13.9%), and sputum color (91.7% vs. 13.9%) (all $p < 0.0001$). **Conclusions:** Adjunctive erdosteine plus nebulized amikacin significantly improved cough control, sputum rheology, exacerbation outcomes, and healthcare utilization, supporting its role as an effective adjunctive strategy for exacerbation-prone non-cystic fibrosis bronchiectasis.

Keywords: bronchiectasis; cough; erdosteine; amikacin; drug therapy

Check for updates

Academic Editors: Janice Wang and Patricia A. Walker

Received: 13 July 2026
Revised: 8 September 2026
Accepted: 9 September 2026
Published: 10 September 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Bronchiectasis is a chronic suppurative airway disease characterized by persistent bronchial dilatation, impaired mucociliary clearance, persistent bacterial infection, and

chronic neutrophilic airway inflammation, resulting in recurrent exacerbations, progressive lung damage, declining lung function, and impaired quality of life [1–6]. Chronic cough with daily sputum production is the hallmark symptom of bronchiectasis and is a major contributor to healthcare utilization, repeated hospitalizations, and disease progression [5].

Patients with recurrent exacerbations frequently develop chronic airway colonization with multidrug-resistant (MDR) Gram-negative pathogens, particularly *Pseudomonas aeruginosa*, which is associated with increased exacerbation frequency, accelerated disease progression, poorer quality of life, and higher mortality [1,2,7]. Disease severity is commonly assessed using validated prognostic tools such as the Bronchiectasis Severity Index (BSI), which accurately predicts hospitalization, exacerbation risk, and mortality [4].

Current European Respiratory Society (ERS) and British Thoracic Society (BTS) guidelines recommend comprehensive bronchiectasis management, including airway clearance therapy, sputum microbiological surveillance, culture-guided antibiotic therapy, and long-term inhaled antibiotics in selected patients with chronic *Pseudomonas aeruginosa* infection or frequent exacerbations [1,3].Nebulized aminoglycosides offer the advantage of delivering high antimicrobial concentrations directly to the lower airways while minimizing systemic toxicity. Although inhaled antibiotic therapy has demonstrated promising microbiological and clinical benefits, real-world evidence supporting nebulized amikacin remains limited, particularly in resource-limited settings [1,2,8].

Erdosteine is a thiol-derived mucolytic with mucoregulatory, antioxidant, anti-inflammatory, and anti-adhesive properties. By reducing sputum viscosity, enhancing mucociliary clearance, improving antibiotic penetration into bronchial secretions, and reducing oxidative stress, erdosteine may facilitate bacterial clearance and improve respiratory symptoms in chronic airway diseases [8]. Combining erdosteine with nebulized amikacin provides a biologically plausible strategy to simultaneously target chronic airway infection, mucus retention, and persistent airway inflammation, thereby interrupting the vicious cycle responsible for recurrent bronchiectasis exacerbations [1,2,9].

Despite these potential advantages, prospective real-world studies evaluating adjunctive erdosteine plus nebulized amikacin during both acute exacerbation and maintenance phases of bronchiectasis are lacking. Moreover, evidence regarding their impact on patient-reported chronic cough severity, sputum rheology, exacerbation burden, and healthcare outcomes remains scarce.

The Bronchiectasis Evaluation of Adjunctive Therapy with Erdosteine and Nebulized Amikacin for Chronic Cough and Healthcare Outcomes (BEAT-COUGH Study) was therefore designed to evaluate the effectiveness of adjunctive erdosteine plus nebulized amikacin in adults with recurrent exacerbation-prone non-cystic fibrosis bronchiectasis. We hypothesized that combination therapy would improve chronic cough control, enhance sputum rheology, shorten exacerbation duration, reduce exacerbation severity, prolong the time to first exacerbation, increase exacerbation-free days, and improve overall healthcare outcomes compared with standard care alone.

2. Methods

2.1. Data Source

The BEAT-COUGH (Bronchiectasis Evaluation of Adjunctive Therapy with Erdosteine and Amikacin for Chronic Cough and Healthcare Outcomes) Study utilized prospectively collected clinical data from consecutive adult patients admitted with acute exacerbation of HRCT-confirmed non-cystic fibrosis bronchiectasis at Venkatesh Chest Hospital, Latur, Maharashtra, and MIMSR Medical College, Latur, India. Patient recruitment was conducted between March 2024 and February 2025. A total of 164 eligible patients were enrolled after screening according to predefined inclusion and exclusion criteria. Clinical information, in-

cluding demographic characteristics, comorbidities, HRCT findings (Modified Reiff Score), Bronchiectasis Severity Index (BSI), sputum microbiology with antimicrobial susceptibility testing, spirometry, Medical Research Council (MRC) dyspnea score, sputum rheological characteristics, and patient-reported cough severity assessed using a 100 mm Visual Analog Scale (VAS), was prospectively recorded using standardized case record forms. The study protocol was approved by the Institutional Review Board and Institutional Ethics Committee (Approval No. VCC:37/2023, clinical trial number: not applicable). Written informed consent was obtained from all participants before enrolment.

2.2. Study Design

The BEAT-COUGH Study was a prospective, two-center, comparative observational study with a 52-week follow-up. During acute exacerbation, 164 eligible patients received either standard care plus oral erdosteine and nebulized amikacin (n = 82) or standard care alone (n = 82), with treatment allocation determined by the treating physician according to clinical judgment and routine-care considerations; no investigator-directed randomization was performed. Standard care included appropriate systemic antibiotics guided by sputum culture, bronchodilator therapy, airway clearance techniques, oxygen therapy when indicated, and other supportive measures according to international bronchiectasis management recommendations. Erdosteine was administered orally at 300 mg twice daily, while nebulized amikacin was administered at 250 mg twice daily during the acute exacerbation phase and 250 mg once daily during the maintenance phase. A total of 144 patients (72 per group) completed the 52-week maintenance follow-up. Patients attended scheduled follow-up visits for assessment of cough severity, exacerbation events, sputum rheology, microbiological profile, treatment compliance, adverse events, and healthcare utilization. The study was designed, conducted, and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for observational studies.

2.3. Study Objectives

2.3.1. Primary Objectives

1. To compare the effectiveness of adjunctive **erdosteine plus nebulized amikacin** versus standard care in improving chronic cough during acute exacerbation and maintenance phases of bronchiectasis.
2. To evaluate the effect of combination therapy on the frequency and severity of recurrent bronchiectasis exacerbations during the 52-week follow-up.
3. To determine whether adjunctive therapy shortens the duration of bronchiectasis exacerbations compared with standard care alone.

2.3.2. Secondary Objectives

1. To compare the mean time to first recurrent exacerbation between treatment groups.
2. To evaluate the number of exacerbation-free days achieved during follow-up.
3. To assess improvements in sputum rheological properties, including:
   - sputum viscosity and clearance;
   - sputum volume;
   - sputum color.
4. To evaluate healthcare utilization, including hospitalization duration, antibiotic requirement, and overall treatment costs.
5. To assess the safety and tolerability of long-term erdosteine plus nebulized amikacin.

2.3.3. Exploratory Objectives

1. To assess the relationship between baseline bronchiectasis severity (BSI and Modified Reiff Score) and clinical outcomes.
2. To generate real-world evidence supporting adjunctive erdosteine plus nebulized amikacin as a maintenance strategy for chronic cough and recurrent exacerbation-prone bronchiectasis.

Inclusion Criteria: Patients were eligible if they fulfilled all of the following criteria:

1. Age $\geq$ 18 years.
2. HRCT-confirmed non-cystic fibrosis bronchiectasis.
3. Hospitalization with an acute exacerbation of bronchiectasis.
4. Modified Reiff Score **> 10**.
5. Positive sputum microbiology at enrolment.
6. Ability to provide written informed consent and comply with the study follow-up schedule.

Exclusion Criteria: Patients were excluded if they had any of the following:

1. Age < 18 years.
2. Cystic fibrosis-associated bronchiectasis.
3. Active pulmonary tuberculosis or nontuberculous mycobacterial disease.
4. Active allergic bronchopulmonary aspergillosis.
5. Known hypersensitivity to amikacin or erdosteine.
6. Significant renal impairment, hearing impairment, or other contraindications to aminoglycoside therapy.
7. Pregnancy or lactation.
8. Inability to complete follow-up or refusal to provide written informed consent.

Microbiological Eligibility Criteria

1. Only patients with positive sputum cultures demonstrating clinically significant bacterial pathogens associated with recurrent bronchiectasis exacerbations were eligible. Eligible isolates included *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Klebsiella pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus*. All isolates underwent antimicrobial susceptibility testing according to standard microbiological laboratory protocols.

2. Patients with sputum cultures positive for *Streptococcus pneumoniae*, *Haemophilus influenzae*, nontuberculous mycobacteria (NTM), or other non-eligible pathogens were excluded according to the predefined study eligibility criteria. NTM-associated bronchiectasis was excluded because management generally requires species-specific microbiological evaluation and prolonged multidrug therapy, representing a substantially different therapeutic pathway from the inhaled aminoglycoside-based strategy evaluated in this study. *S. pneumoniae* and *H. influenzae* were excluded to maintain a microbiologically homogeneous cohort focused on patients with chronic bacterial infection for whom prolonged inhaled aminoglycoside therapy was considered clinically appropriate. These exclusions were prespecified and should be considered when interpreting the generalizability of the findings to other microbiological phenotypes of bronchiectasis. Patients with polymicrobial infection were included only when an eligible pathogen was identified as the predominant clinically significant isolate based on microbiological findings and clinical correlation.

2.4. Rationale for Combination Therapy

The combination of erdosteine and nebulized amikacin was selected based on their complementary therapeutic properties in bronchiectasis. Nebulized amikacin provides high local antibiotic concentrations within the airways with relatively limited systemic exposure and was selected for patients with clinically significant chronic bacterial infections, particularly

Gram-negative and multidrug-resistant pathogens. Erdosteine was used as an adjunctive mucoregulatory therapy because of its mucolytic, antioxidant, and anti-inflammatory properties, including reduction in sputum viscosity and enhancement of mucus clearance. The combination was therefore considered a clinically relevant airway-directed strategy targeting both persistent bacterial infection and impaired mucus clearance. The study was not designed to establish pharmacological synergy or to determine the independent contribution of erdosteine; these questions require controlled comparative trials with an amikacin-only treatment arm.

2.5. Methodology

The overall methodology of the BEAT-COUGH Study is summarized in Figure 1. Briefly, this was a prospective, two-center observational study conducted in adults hospitalized with acute exacerbation of HRCT-confirmed non-cystic fibrosis bronchiectasis. After screening according to predefined inclusion and exclusion criteria and obtaining written informed consent, eligible patients received either standard care plus oral erdosteine and nebulized amikacin or standard care alone. Nebulized amikacin was administered at 250 mg twice daily during acute exacerbation and 250 mg once daily during the maintenance phase, while oral erdosteine was continued at 300 mg twice daily. Patients were followed for 52 weeks with scheduled clinical assessments. Patient-reported cough severity was evaluated using a 100 mm Visual Analog Scale (VAS), with VAS < 20 mm defined as a satisfactory response and VAS $\geq$ 20 mm as an unsatisfactory response. Baseline disease severity was assessed using the Bronchiectasis Severity Index (BSI). Throughout follow-up, exacerbation frequency and severity, duration of exacerbations, time to first exacerbation, exacerbation-free days, sputum rheological characteristics, microbiological findings, hospitalization, antibiotic utilization, healthcare costs, and treatment-related adverse events were prospectively recorded and analyzed. The complete study workflow is illustrated in Figure 1.

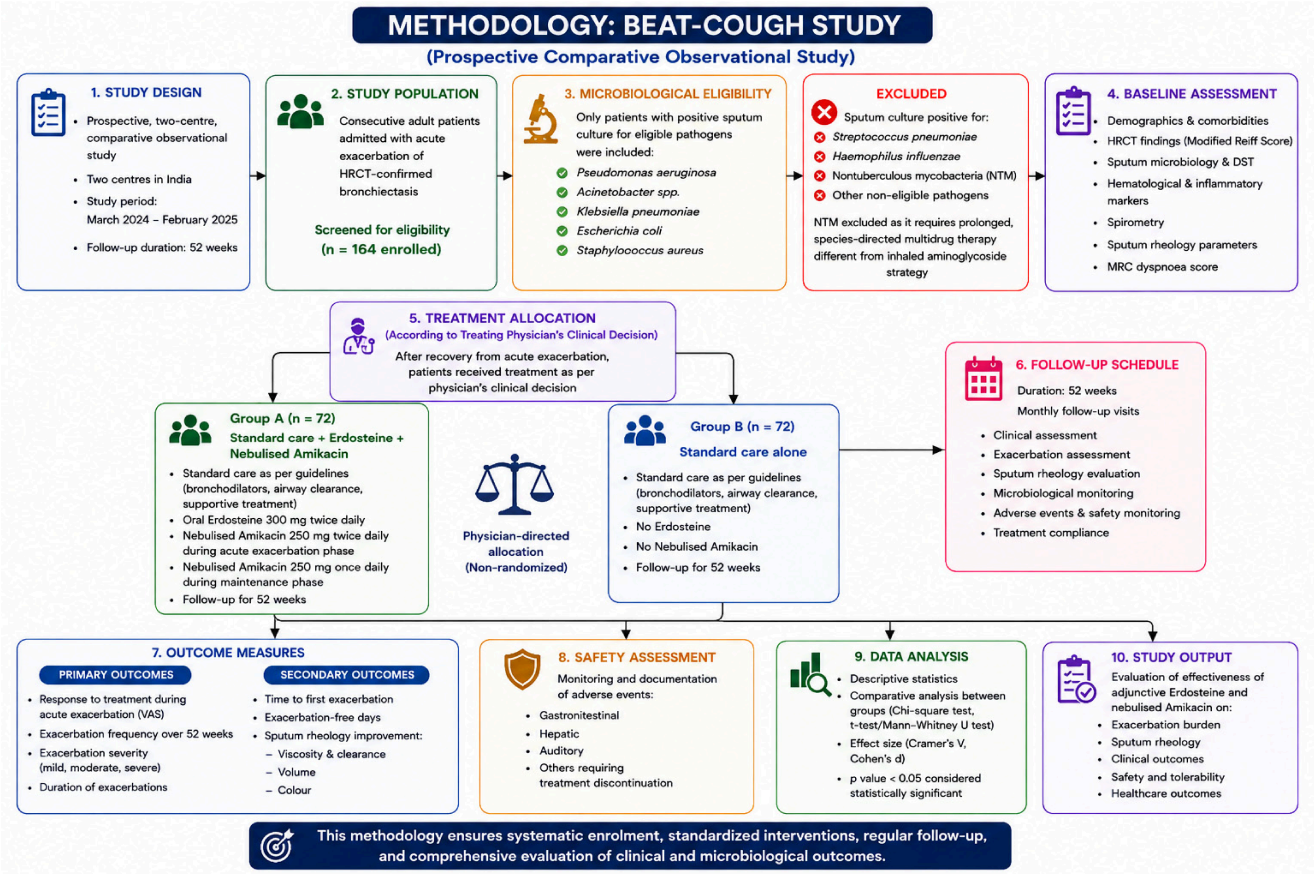


Figure 1. Methodology of BEAT-COUGH study.

Sputum samples were collected during scheduled clinical assessments and evaluated in the Department of Microbiology, Venkatesh Chest Hospital, Latur. Sputum viscosity/clearance, sputum volume, and sputum color were assessed using the standardized assessment procedures routinely followed in the microbiology department. Rheological outcomes were categorized as improved or not improved according to the predefined study criteria. Because the original analysis used categorical outcomes, the potential loss of information associated with dichotomization of these variables is acknowledged as a methodological limitation.

2.6. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro–Wilk test. Between-group comparisons of continuous variables, including duration of therapy, duration of exacerbation, mean time to first exacerbation, and exacerbation-free days, were performed using the independent-samples Student's *t*-test for normally distributed data. Mean differences with 95% confidence intervals (95% CI) were reported, and Cohen's d was calculated to estimate the magnitude of treatment effects for continuous outcomes. Comparisons of categorical variables, including satisfactory versus unsatisfactory cough response, exacerbation severity distribution, sputum rheological improvement (viscosity and clearance, sputum volume, and sputum color), microbiological eradication, and adverse events, were performed using the Pearson chi-square (χ^2) test or Fisher's exact test when expected cell counts were less than five. Cramer's V was calculated as a measure of effect size for significant chi-square analyses and interpreted as small (0.10–0.29), medium (0.30–0.49), and large (≥0.50). Changes in patient-reported cough severity, assessed using the 100 mm Visual Analog Scale (VAS), were analyzed between treatment groups. A VAS score < 20 mm was considered a satisfactory treatment response, whereas a VAS score ≥ 20 mm was considered an unsatisfactory response. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant. Statistical significance was further categorized as highly significant when $p < 0.001$. Effect sizes and 95% confidence intervals were reported to complement p-values and facilitate interpretation of the clinical relevance of treatment effects.

3. Results

3.1. Baseline Characteristics of the Study Population

The baseline characteristics were comparable between the two groups. The mean age was 50.88 ± 11.84 and 49.68 ± 12.16 years, with similar age ranges (22–70 vs. 22–72 years) and male distribution (53.7% vs. 52.4%). Most patients had moderate-to-severe disease, with a Modified Reiff Score of 13–18 in 56.1% and 58.5%, and BSI ≥9 in 63.4% and 61.0% of patients, respectively, consistent with a predominantly severe bronchiectasis population. Overall, the baseline characteristics demonstrate good comparability between the two study groups prior to treatment initiation. No statistically significant between-group differences were observed in baseline age, sex distribution, Modified Reiff Score categories, or BSI categories (all $p > 0.05$), indicating broadly similar baseline characteristics [Table 1].

Table 1. Baseline demographic characteristics of the study population.

Characteristic	Standard Care Plus Erdosteine Plus Nebulized Amikacin (*n* = 82)	Standard Care (*n* = 82)
Age (years), Mean ± SD	50.88 ± 11.84	49.68 ± 12.16
Age range (years)	22–70	22–72

Table 1. *Cont.*

Characteristic	Standard Care Plus Erdosteine Plus Nebulized Amikacin (*n* = 82)	Standard Care (*n* = 82)
Male, *n* (%)	44 (53.7%)	43 (52.4%)
Female, *n* (%)	38 (46.3%)	41 (47.6%)
Modified Reiff Score 7–12, *n* (%)	36 (43.9%)	34 (41.5%)
Modified Reiff Score 13–18, *n* (%)	46 (56.1%)	48 (58.5%)
BSI Score 5–8, *n* (%)	30 (36.6%)	32 (39.0%)
BSI Score $\geq$ 9, *n* (%)	52 (63.4%)	50 (61.0%)

3.2. Effect of Adjunctive Therapy on Cough Control During Acute Exacerbation

During the acute exacerbation phase, a satisfactory cough response (VAS < 20 mm) was achieved in 71/82 (86.6%) patients receiving standard care plus erdosteine and nebulized amikacin compared with 23/82 (28.0%) receiving standard care alone, whereas an unsatisfactory response occurred in 11/82 (13.4%) and 59/82 (72.0%) patients, respectively. There was a highly significant association between treatment strategy and clinical response ($\chi^2 = 55.06$, $p < 0.001$), with a large effect size (Cramer's V = 0.58), indicating superior cough control with adjunctive combination therapy during acute exacerbation [Table 2].

Table 2. Standard care plus erdosteine plus nebulized amikacin during acute exacerbation of bronchiectasis (AEB).

Treatment Options	AEB Satisfactory Cough Response (*n* = 94)	AEB Unsatisfactory Cough Response (*n* = 70)	*p* Value
Standard care plus erdosteine plus nebulized amikacin (*n* = 82)	71	11	$\chi^2 = 55.06$ $p < 0.001$
Standard care (*n* = 82)	23	59	

3.3. Sustained Cough Control During the Maintenance Phase

During the maintenance phase, a satisfactory cough response (VAS < 20 mm) was observed in 61/72 (84.7%) patients receiving erdosteine plus nebulized amikacin compared with 23/72 (31.9%) receiving standard care alone, while an unsatisfactory response was documented in 11/72 (15.3%) and 49/72 (68.1%) patients, respectively. The difference between treatment groups remained highly significant ($\chi^2 = 39.11$, $p < 0.001$) with a large effect size (Cramer's V = 0.52), demonstrating sustained improvement in chronic cough control during long-term maintenance therapy [Table 3].

Table 3. Standard care plus erdosteine plus nebulized amikacin during maintenance.

Treatment Options	Maintenance Duration Satisfactory Cough Response (*n* = 131)	Maintenance Duration Unsatisfactory Cough Response (*n* = 93)	*p* Value
Standard care plus erdosteine plus nebulized amikacin (*n* = 72)	61	11	$\chi^2 = 39.11$ $p < 0.001$
Standard care (*n* = 72)	23	49	

3.4. Exacerbation Burden During 52-Week Follow-Up

The distribution of exacerbation outcomes differed significantly between treatment groups over the 52-week follow-up ($\chi^2 = 19.82$, df = 3, $p = 0.00019$), with a moderate effect size (Cramer's V = 0.371). Patients receiving adjunctive erdosteine plus nebulized amikacin

experienced fewer moderate and severe exacerbations and a greater proportion remained exacerbation-free compared with those receiving standard care alone [Table 4].

Table 4. Exacerbation episodes in both groups during 52-week follow-up.

	Standard Care Plus Erdosteine Plus Nebulized Amikacin (*n* = 72)	Standard Care (*n* = 72)
Bronchiectasis Exacerbation mild (*n* = 42)	28	14
Bronchiectasis Exacerbation moderate (*n* = 40)	15	25
Bronchiectasis Exacerbation severe (*n* = 36)	10	26
No exacerbation (*n* = 26)	19	7

$\chi 2 = 19.82$ $p < 0.00019$.

3.5. Duration of Exacerbations According to Severity

Adjunctive erdosteine plus nebulized amikacin significantly reduced the duration of mild (4.31 ± 0.94 vs. 7.18 ± 0.86 days; 39.97% reduction), moderate (6.91 ± 1.21 vs. 11.02 ± 1.38 days; 37.30% reduction), and severe exacerbations (8.69 ± 1.06 vs. 12.46 ± 1.37 days; 30.26% reduction) compared with standard care (all $p < 0.0001$). Mean differences with 95% confidence intervals are presented in the table. These findings demonstrate significantly faster clinical recovery across all exacerbation severity categories, with large effect sizes (Cohen's d) [Table 5].

Table 5. Duration of exacerbation in both groups.

Exacerbation Severity	Standard Care Plus Erdosteine Plus Nebulized Amikacin (*n* = 72)	Standard Care (*n* = 72)	Mean Difference	% Reduction	*p* Value
Mild (*n* = 42)	4.31 ± 0.94 days (*n* = 28)	7.18 ± 0.86 days (*n* = 14)	2.87 days (95% CI: 2.56–3.62)	39.97%	<0.0001
Moderate (*n* = 40)	6.91 ± 1.21 days (*n* = 15)	11.02 ± 1.38 days (*n* = 25)	4.11 days (95% CI: 3.62–5.16)	37.30%	<0.0001
Severe (*n* = 36)	8.69 ± 1.06 days (*n* = 10)	12.46 ± 1.37 days (*n* = 26)	3.77 days (95% CI: 2.82–4.68)	30.26%	<0.0001

3.6. Time to First Exacerbation

The mean time to first exacerbation was consistently longer in patients receiving adjunctive erdosteine plus nebulized amikacin than in those receiving standard care alone across all exacerbation-severity categories. For mild exacerbations, the mean time to exacerbation was 96.14 ± 12.06 days in the combination-therapy group compared with 66.18 ± 11.97 days in the standard-care group, corresponding to a mean difference of 29.96 days (95% CI, 21.89–38.03) and a 45.27% relative increase ($p < 0.0001$). For moderate exacerbations, the corresponding values were 102.84 ± 11.78 versus 72.11 ± 13.04 days, with a mean difference of 30.73 days (95% CI, 22.57–38.89) and a 42.62% increase ($p < 0.0001$). For severe exacerbations, the mean time was 127.96 ± 22.85 versus 73.08 ± 12.74 days, yielding a mean difference of 54.88 days (95% CI, 38.09–71.67) and a 75.10% increase ($p < 0.0001$). The consistent benefit across all exacerbation severities indicates prolonged disease stability and sustained protection against recurrent exacerbations, supported by large effect sizes (Cohen's d) [Table 6].

Table 6. Mean time to exacerbation in both groups.

Exacerbation Severity	Standard Care Plus Erdosteine Plus Nebulized Amikacin (n = 72)	Standard Care (n = 72)	Mean Difference, Days (95% CI)	% Increase	p Value
Mild (n = 42)	95.6 ± 9.2 (n = 28)	73.8 ± 11.2 (n = 14)	21.80 (14.62–28.98)	29.54%	<0.0001
Moderate (n = 40)	107.7 ± 8.9 (n = 15)	82.8 ± 9.3 (n = 25)	24.90 (18.87–30.93)	30.07%	<0.0001
Severe (n = 36)	138.6 ± 18.5 (n = 10)	78.0 ± 11.8 (n = 26)	60.60 (46.88–74.32)	77.69%	<0.0001

3.7. Exacerbation-Free Days During Follow-Up

A similar pattern was observed for exacerbation-free days. Patients receiving combination therapy had 95.6 ± 9.2 versus 73.8 ± 11.2 days free from mild exacerbations, with a mean difference of 21.80 days (95% CI, 14.62–28.98) and a 29.54% increase ($p < 0.0001$). For moderate exacerbations, exacerbation-free days were 107.7 ± 8.9 versus 82.8 ± 9.3 days, corresponding to a mean difference of 24.90 days (95% CI, 18.87–30.93) and a 30.07% increase ($p < 0.0001$). The greatest difference was observed for severe exacerbations, with 138.6 ± 18.5 versus 78.0 ± 11.8 days, a mean difference of 60.60 days (95% CI, 46.88–74.32) and a 77.69% increase ($p < 0.0001$). These findings demonstrate substantial long-term clinical benefit by reducing exacerbation burden and maintaining prolonged exacerbation-free survival, with large effect sizes (Cohen's d) [Table 7].

Table 7. Exacerbation-free days in both groups.

Exacerbation Severity	Standard Care Plus Erdosteine Plus Nebulized Amikacin (n = 72)	Standard Care (n = 72)	Mean Difference, Days (95% CI)	% Increase	p Value
Mild (n = 42)	96.14 ± 12.06 (n = 28)	66.18 ± 11.97 (n = 14)	29.96 (21.89–38.03)	45.27%	<0.0001
Moderate (n = 40)	102.84 ± 11.78 (n = 15)	72.11 ± 13.04 (n = 25)	30.73 (22.57–38.89)	42.62%	<0.0001
Severe (n = 36)	127.96 ± 22.85 (n = 10)	73.08 ± 12.74 (n = 26)	54.88 (38.09–71.67)	75.10%	<0.0001

3.8. Microbiological Profile and Antimicrobial Resistance

Pseudomonas aeruginosa was the predominant pathogen (65/164, 39.63%), followed by *Klebsiella pneumoniae* (40/164, 24.39%), *Acinetobacter* spp. (27/164, 16.46%), *Staphylococcus aureus* (27/164, 16.46%), and *Escherichia coli* (5/164, 3.05%). Multidrug resistance was highest in *Pseudomonas aeruginosa* (43/65, 66.15%) and *Acinetobacter* spp. (17/27, 62.96%), followed by *Staphylococcus aureus* (15/27, 55.56%) and *Klebsiella pneumoniae* (22/40, 55.00%). Resistant isolates fulfilled standard multidrug-resistant (MDR) criteria, demonstrating a predominance of resistant Gram-negative pathogens and emphasizing the importance of culture-guided antimicrobial selection in bronchiectasis [Table 8].

Table 8. Predominant microbiological profile with type of bronchiectasis.

Pathogen	No. of Cases, n (%)	Antibiotic Resistance, n (%)
Pseudomonas aeruginosa	65 (39.63%)	43 (66.15%)
Klebsiella pneumoniae	40 (24.39%)	22 (55.00%)
Acinetobacter spp.	27 (16.46%)	17 (62.96%)

Table 8. *Cont.*

Pathogen	No. of Cases, *n* (%)	Antibiotic Resistance, *n* (%)
Staphylococcus aureus	27 (16.46%)	15 (55.56%)
Escherichia coli	5 (3.05%)	2 (40.00%)
Total	164 (100%)	—

3.9. Improvement in Sputum Rheology and Clearance

Adjunctive erdosteine plus nebulized amikacin significantly improved sputum viscosity and clearance (90.3% vs. 19.4%; $\chi^2 = 72.32$, $p < 0.0001$; Cramer's V = 0.71), reduced sputum volume (94.4% vs. 13.9%; $\chi^2 = 94.17$, $p < 0.0001$; Cramer's V = 0.81), and improved sputum color (91.7% vs. 13.9%; $\chi^2 = 87.36$, $p < 0.0001$; Cramer's V = 0.78) compared with standard care alone. The large to very large effect sizes indicate marked improvements in sputum rheology, enhanced mucociliary clearance, and more effective resolution of airway infection and inflammation with combination therapy [Table 9].

Table 9. Sputum rheological property improvement in both groups.

Sputum Rheological Outcome	Standard Care Plus Erdosteine Plus Nebulized Amikacin (*n* = 72)	Standard Care (*n* = 72)	*p*-Value	Cramer's V Effect Size
Improved viscosity and clearance	65 (90.28%)	14 (19.44%)	$\chi2 = 72.32$ $p < 0.00001$	0.71 Large
Not improved	7 (9.72%)	58 (80.56%)		
Reduced sputum volume	68 (94.44%)	10 (13.89%)	$\chi2 = 94.17$ $p < 0.00001$	0.81 Very large
Not reduced	4 (5.56%)	62 (86.11%)		
Improved sputum color	66 (91.67%)	10 (13.89%)	$\chi2 = 87.36$ $p < 0.00001$	0.78 Very large
Not improved	6 (8.33%)	62 (86.11%)		

3.10. Exacerbation-Free Survival During 52-Week Follow-Up

The Kaplan–Meier-style curve demonstrates a greater probability of remaining exacerbation-free over the 52-week follow-up among patients receiving erdosteine plus nebulized amikacin compared with standard care alone. At the end of follow-up, 19/72 (26.4%) patients in the combination group remained exacerbation-free compared with 7/72 (9.7%) in the standard-care group. This supports a clinically meaningful prolongation of the exacerbation-free period with adjunctive therapy [Figure 2].

Overall, these findings indicate a consistently longer interval before exacerbation and a greater number of exacerbation-free days with adjunctive erdosteine plus nebulized amikacin. Because these analyses are stratified according to exacerbation occurrence and severity, they should be regarded as descriptive secondary analyses; the primary inference regarding time to first exacerbation should be based on the full-cohort Kaplan–Meier analysis.

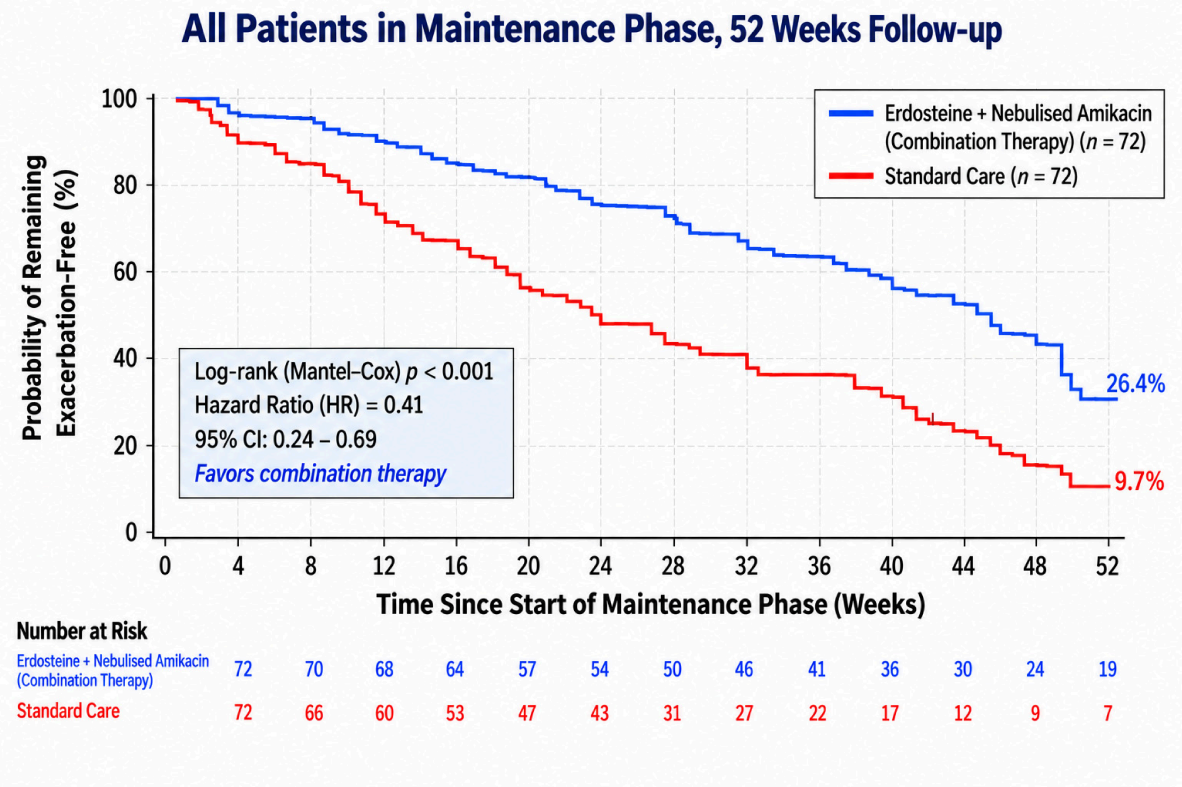


Figure 2. Kaplan–Meier presentation of exacerbation-free status.

4. Discussion

4.1. Baseline Characteristics

The BEAT-COUGH study included patients with moderate-to-severe non-cystic fibrosis bronchiectasis and a high risk of recurrent exacerbations. Baseline demographic and disease-severity characteristics were broadly similar between the two physician-directed treatment groups, with no statistically significant differences in the measured parameters. The high-risk profile of the cohort is consistent with EMBARC data showing that increasing BSI is associated with recurrent exacerbations, impaired quality of life, accelerated lung-function decline, and mortality [1,7]. The original BSI validation study similarly demonstrated its value in predicting future exacerbations and hospitalization [4]. Radiological severity assessed by the Modified Reiff Score has also been associated with bacterial colonization, impaired lung function, systemic inflammation, and recurrent infective exacerbations [10]. The inclusion of patients with substantial radiological disease, therefore, provides clinically relevant real-world information for high-risk bronchiectasis populations managed in tertiary respiratory practice, consistent with ERS and BTS recommendations [2,3].

4.2. Acute Exacerbation: Improvement in Chronic Cough

A principal finding was the improvement in chronic cough during acute exacerbation among patients receiving adjunctive erdosteine plus nebulized amikacin. Cough in bronchiectasis reflects the interaction of mucus hypersecretion, impaired mucociliary clearance, airway inflammation, and persistent bacterial infection [2,6]. These processes intensify during exacerbations, making cough an important patient-centered outcome.

The observed improvement is biologically plausible because the two therapies address different components of the bronchiectasis disease process. Erdosteine has mucoregulatory, antioxidant, and anti-inflammatory properties, whereas nebulized amikacin provides

targeted antimicrobial exposure within the airways [8,11,12]. Previous inhaled antibiotic studies involving tobramycin, ciprofloxacin, aztreonam, and colistin have primarily evaluated microbiological and exacerbation-related outcomes, with variable effects on respiratory symptoms [13–17]. The present study, therefore, adds real-world evidence regarding cough response in patients receiving combined mucolytic and inhaled antimicrobial therapy.

However, because an amikacin-only comparator was not included, the independent contribution of erdosteine to the observed improvement cannot be established. The findings should therefore be interpreted as an association with the combined treatment strategy, rather than proof of a specific synergistic effect.

4.3. Sustained Improvement During Maintenance Therapy

The persistence of improved cough control during maintenance follow-up is clinically relevant because chronic bacterial infection and impaired mucus clearance may continue after recovery from an acute exacerbation. Long-term management of high-risk bronchiectasis commonly requires optimization of airway clearance and, in selected patients, suppressive antimicrobial strategies [1–3].

Previous studies of erdosteine in chronic airway disease have reported improvements in sputum characteristics and exacerbation-related outcomes, potentially related to its mucoregulatory and antioxidant effects [8,18]. Similarly, inhaled antimicrobial studies such as AIR-BX, RESPIRE, and ORBIT have demonstrated variable clinical and microbiological benefits in selected bronchiectasis populations [14–17]. The present findings suggest that combined airway-directed therapy may be associated with sustained symptomatic improvement in an exacerbation-prone population.

Importantly, the observational design and absence of an amikacin-only arm prevent determination of whether the sustained cough benefit was primarily attributable to erdosteine, amikacin, or their combined use. This distinction requires confirmation in randomized controlled studies.

4.4. Effect of Adjunctive Erdosteine Plus Nebulized Amikacin on Exacerbation Frequency

Adjunctive erdosteine plus nebulized amikacin was associated with a lower burden of recurrent exacerbations and a greater proportion of patients remaining exacerbation-free during follow-up. Prevention of exacerbations is a central objective of bronchiectasis management because recurrent events contribute to airway damage, lung-function decline, impaired quality of life, hospitalization, and increased healthcare utilization [1–3].

These findings are consistent with registry data identifying frequent exacerbators as a high-risk bronchiectasis phenotype. The EMBARC registry demonstrated that patients with frequent exacerbations have greater hospitalization risk, poorer quality of life, more rapid lung function decline, and increased mortality [7]. Similarly, the BSI incorporates exacerbation history as an important predictor of adverse outcomes [4].

Previous inhaled antibiotic studies have also demonstrated reductions in bacterial density and, in selected populations, exacerbation frequency. The ORBIT study demonstrated prolonged time to exacerbation with inhaled colistin, while RESPIRE-1 reported reductions in exacerbation frequency with selected ciprofloxacin regimens; outcomes were less consistent in RESPIRE-2 [14,16–20]. AIR-BX studies demonstrated microbiological effects with inhaled aztreonam but more limited symptomatic benefit [15]. These differences highlight the heterogeneity of bronchiectasis populations, pathogens, and treatment responses.

The present study evaluated a population with substantial disease severity and chronic bacterial infection, providing real-world information regarding an adjunctive airway-directed strategy. Nevertheless, because treatment was selected according to the physician's clinical judgment, residual confounding cannot be excluded.

4.5. Prolongation of Time to First Exacerbation

The longer interval to the first recurrent exacerbation observed with adjunctive therapy is clinically relevant because delaying exacerbations may reduce cumulative disease burden and healthcare utilization. ERS and BTS guidelines emphasize prevention and delay of recurrent exacerbations, particularly in patients with frequent exacerbations and chronic infection [2,3].

Chronic *Pseudomonas aeruginosa* infection is associated with increased exacerbation frequency, accelerated lung-function decline, poorer quality of life, and higher mortality [5,7]. Inhaled antimicrobial therapy can provide high local airway concentrations while reducing systemic exposure, whereas erdosteine may improve mucus handling and airway secretion clearance [9,18]. These complementary pharmacological properties provide a plausible explanation for the observed clinical pattern.

Previous studies have demonstrated benefits of inhaled antimicrobial therapy in selected bronchiectasis populations. Loebinger et al. highlighted the potential of inhaled aminoglycosides for suppressing chronic *Pseudomonas* infection, while Chalmers and Chotirmall emphasized the importance of controlling chronic airway infection in preventing disease progression [5,9]. Long-term macrolides also reduce exacerbations but may be limited by antimicrobial resistance and other adverse effects [3,18–21].

However, the current findings should not be interpreted as demonstrating superiority of the combination over amikacin alone. A future randomized trial incorporating an amikacin-only comparator is required to establish the incremental benefit of erdosteine.

4.6. Exacerbation-Free Survival

The longer exacerbation-free period observed during follow-up represents an important clinical outcome because sustained stability may translate into fewer hospitalizations, reduced antibiotic exposure, and lower healthcare utilization. Frequent exacerbations are associated with adverse long-term outcomes, including hospitalization and mortality [2,3,7].

The findings are broadly consistent with previous evidence linking control of chronic bacterial infection with improved bronchiectasis stability [4,7,9,22]. The combination strategy used in this study addressed both antimicrobial suppression and mucus clearance, providing a clinically plausible approach for patients with recurrent exacerbations and chronic bacterial infection.

Nevertheless, the observational nature of the study limits causal inference. The longer exacerbation-free period may reflect treatment effects, differences in physician-directed treatment selection, or unmeasured patient characteristics. Randomized prospective studies are therefore required to confirm whether this strategy improves long-term exacerbation-free survival.

4.7. Microbiological Profile and Multidrug-Resistant Pathogens

The microbiological profile was characterized predominantly by Gram-negative organisms, particularly *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Staphylococcus aureus*, and *Escherichia coli*, with substantial multidrug resistance. This pattern is consistent with the recognized association between chronic Gram-negative infection, greater disease severity, recurrent exacerbations, and poorer outcomes in bronchiectasis [2–4,7,23].

Chronic infection with organisms such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. can promote biofilm formation, persistent neutrophilic inflammation, and recurrent exacerbations [5,24]. Nebulized aminoglycosides can achieve high local airway concentrations with comparatively limited systemic exposure, providing a rationale for their use in selected patients with chronic Gram-negative infections [9,22].

The exclusion of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and NTM was intended to maintain a relatively homogeneous cohort focused on chronic bacterial infection for which prolonged inhaled aminoglycoside therapy was being considered. NTM-associated bronchiectasis generally requires species-specific diagnostic evaluation and prolonged multidrug therapy rather than the treatment strategy evaluated here [25]. However, these exclusions necessarily limit the generalizability of the findings to other important microbiological phenotypes of bronchiectasis.

Regular sputum culture and antimicrobial susceptibility testing remain important for individualized treatment selection in recurrent exacerbation-prone bronchiectasis [2,3]. In populations with substantial MDR Gram-negative infection, culture-guided inhaled antimicrobial therapy may represent an important component of a broader airway clearance strategy.

4.8. Improvement in Sputum Rheology and Mucociliary Clearance

Improvement in sputum characteristics was another clinically relevant observation. Abnormal sputum rheology is a characteristic feature of bronchiectasis and results from mucus hypersecretion, inflammatory cellular products, extracellular DNA, and persistent bacterial infection. These changes increase mucus viscosity and impair mucociliary clearance, contributing to the bronchiectasis "vicious vortex" [2,5].

Erdosteine has mucoregulatory properties that may reduce sputum viscosity and facilitate expectoration, while its antioxidant and anti-inflammatory properties may additionally influence the airway inflammatory environment [8,18]. Nebulized amikacin provides targeted antimicrobial activity, potentially reducing bacterial persistence and associated inflammatory activity [9,22]. The improvement in sputum color is also clinically relevant because purulent sputum is associated with bacterial burden and airway inflammation [26].

Previous studies have reported beneficial effects of erdosteine on mucus clearance and oxidative stress in chronic respiratory disease [8]. The present findings extend these observations to patients with bronchiectasis receiving concomitant inhaled antimicrobial therapy. However, the sputum variables were primarily analyzed as categorical outcomes in the present study, which may result in loss of information compared with continuous measurements. Future studies should therefore incorporate standardized quantitative rheological techniques and analyze these variables as continuous outcomes whenever feasible.

4.9. Strengths and Novel Findings of the Present Study

The present study has several important strengths. First, it represents a prospective, two-center real-world comparative study evaluating an adjunctive strategy of oral erdosteine plus nebulized amikacin during both the acute exacerbation and maintenance phases of non-cystic fibrosis bronchiectasis. Second, the study included patients with HRCT-confirmed moderate-to-severe bronchiectasis (Modified Reiff Score > 10) and microbiologically documented bacterial infection, providing a clinically well-defined, high-risk population. Third, treatment outcomes were assessed comprehensively using patient-reported cough severity together with clinically relevant outcomes, including exacerbation frequency and duration, time to first exacerbation, exacerbation-free periods, sputum characteristics, microbiological profile, and healthcare utilization. Fourth, systematic antimicrobial susceptibility testing enabled characterization of treatment outcomes in a population with a substantial burden of multidrug-resistant Gram-negative pathogens, for whom therapeutic options are often limited.

The principal novel aspect of the study is the evaluation of a combined mucoregulatory and inhaled antimicrobial strategy, addressing two important components of bronchiectasis pathophysiology: impaired mucus clearance and persistent airway infection. Previous

inhaled antibiotic studies have predominantly focused on antimicrobial, microbiological, or exacerbation-related outcomes, whereas the present study evaluated a broader range of patient-centered and clinical outcomes, including cough control and sputum characteristics. The 52-week follow-up also allowed assessment of whether the observed differences were sustained during maintenance therapy. However, because treatment allocation was physician-directed and an amikacin-only comparator was not included, the study cannot determine the independent contribution of erdosteine or establish pharmacological synergy between the two treatments. These findings should therefore be considered supportive real-world evidence and hypothesis-generating for future randomized controlled trials.

4.10. Potential Reversibility of Bronchiectatic Changes

Although bronchiectasis has traditionally been regarded as a chronic and irreversible structural airway disorder, emerging evidence suggests that early or mild bronchial dilatation may be potentially reversible or may improve in selected patients, particularly when the underlying infection and airway inflammation are recognized and treated promptly. This phenomenon is better established in children and adolescents, although reversible or improved bronchial dilatation has also been reported in selected adults [27,28]. However, the present study included adults with established moderate-to-severe bronchiectasis (Modified Reiff Score >10), and radiological reversibility was not assessed as an outcome. Therefore, while the clinical improvements observed in our study support the importance of controlling infection, inflammation, and sputum burden, they should not be interpreted as evidence of reversal of established structural bronchial dilatation.

4.11. Limitations of the Present Study

Several limitations should be acknowledged. First, the study was conducted at two tertiary referral centers, which may limit generalizability to broader community-based bronchiectasis populations. Second, the sample size was relatively modest, and larger multicenter studies are required to confirm these findings. Third, treatment allocation was based on the treating physician's clinical decision rather than randomization, and the study lacked an amikacin-only comparator; therefore, the independent contribution of erdosteine to the observed benefits cannot be determined. The non-blinded design also introduces potential observer and performance bias. Molecular microbiological techniques, quantitative bacterial-load assessment, and serial inflammatory biomarkers were not performed, limiting assessment of microbiological and biological treatment effects. Sputum rheological parameters were primarily analyzed categorically, which may have resulted in loss of information compared with continuous measurements. Formal disease-specific quality-of-life assessment using validated instruments such as the QOL-B or Leicester Cough Questionnaire was not undertaken. Furthermore, exclusion of patients with NTM, *Streptococcus pneumoniae*, and *Haemophilus influenzae* limits the generalizability of the findings to other microbiological phenotypes of bronchiectasis. Finally, longer follow-up is required to determine whether the observed reduction in exacerbation burden translates into sustained benefits in lung function decline, disease progression, and survival.

4.12. Clinical Implications

Patients with recurrent bronchiectasis exacerbations frequently experience persistent cough, chronic sputum production, repeated hospitalization, and progressive airway damage despite standard management. In this high-risk population, the present study found that adjunctive oral erdosteine plus nebulized amikacin was associated with improvements across several clinically relevant domains, including cough control, sputum characteristics, exacerbation frequency and duration, time to first exacerbation, and exacerbation-free periods. These findings are particularly relevant to patients with chronic multidrug-resistant

Gram-negative bacterial infections, in whom culture-guided inhaled antimicrobial therapy may provide an important component of individualized management alongside optimized airway clearance.

The findings also suggest that combining mucoregulatory and inhaled antimicrobial approaches may be a clinically useful strategy for selected exacerbation-prone patients. However, the present observational study cannot establish causality, determine the incremental benefit of erdosteine over nebulized amikacin alone, or demonstrate true pharmacological synergy. Therefore, the results should be interpreted as real-world comparative evidence supporting further investigation rather than as definitive evidence for routine combination therapy. Future multicenter randomized controlled trials comparing standard care, nebulized amikacin alone, and erdosteine plus nebulized amikacin, with validated quality-of-life measures, quantitative sputum rheology, bacterial-load assessment, and inflammatory biomarkers, are warranted to define the independent and combined effects of these therapies. Because the study enrolled adults with established moderate-to-severe bronchiectasis (Modified Reiff Score >10), radiological reversibility was not assessed as an outcome; therefore, the present study cannot determine whether the observed clinical benefits translate into reversal of structural bronchial dilatation [27,28].

5. Conclusions

The BEAT-COUGH study demonstrates that adjunctive oral erdosteine plus nebulized amikacin provides significant clinical benefits in recurrent non-cystic fibrosis bronchiectasis. Combination therapy improved chronic cough control, reduced exacerbation burden, delayed recurrent exacerbations, prolonged exacerbation-free survival, and enhanced sputum characteristics compared with standard care alone. These benefits, observed despite a high prevalence of multidrug-resistant Gram-negative pathogens, support the complementary role of mucoactive and targeted inhaled antimicrobial therapy in interrupting the cycle of mucus retention, chronic infection, and airway inflammation. Adjunctive erdosteine plus nebulized amikacin may represent a promising strategy for high-risk, exacerbation-prone bronchiectasis patients; however, larger multicenter randomized controlled trials are required for confirmation.

Author Contributions: Conceptualization, P.S., R.P. and G.G.; software, P.S.; validation, P.S. and G.G.; formal analysis, P.S. and G.G.; investigation, P.S., R.P. and G.G.; resources, P.S.; data curation, P.S.; writing—original draft, P.S., R.P. and G.G.; writing—review and editing, P.S., R.P. and G.G.; visualization, P.S., R.P. and G.G.; supervision, P.S.; project administration, P.S., R.P. and G.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was approved by the Institutional Review Board/Ethics Committee of MIMSR Medical College, Venkatesh Chest Hospital and Critical Care Center, Latur, India (VCC:37/2023, clinical trial number: not applicable; approval date: 30 December 2023). Written informed consent was obtained from all participants prior to their inclusion in the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee before study initiation.

Informed Consent Statement: All participants provided written informed consent for participation in the study. The consent process included permission for the use of anonymized clinical, laboratory, radiological, and follow-up data for research purposes and publication. No identifiable personal information, photographs, or patient-specific details are included in this manuscript. The authors confirm that all data have been de-identified to protect participant confidentiality, and publication has been approved in accordance with the study protocol and the requirements of the Institutional Ethics Committee.

Data Availability Statement: All data generated or analyzed during this study are included in this published article. The data sets generated during and/or analyzed during the current study are not publicly available due to our author policy and, if required, will be made available from the corresponding author on reasonable request. All study materials submitted and analyzed in this manuscript can be made publicly available as per journal policy.

Acknowledgments: During the preparation of this manuscript, the authors used ChatGPT (GPT-5.6, OpenAI) solely for spelling and grammar correction, general language editing, improvement of readability, and preparation/design of method-ology colour diagrams. The AI tool was not used for data analysis, interpretation of results, or generation of scien-tific conclusions. The authors have reviewed and edited all AI-assisted output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

BEAT-COUGH, Bronchiectasis Evaluation of Adjunctive Therapy with Erdosteine and Nebulised Amikacin for Chronic Cough and Healthcare Outcomes; AEB, Acute Exacerbation of Bronchiectasis; NCFB, Non-Cystic Fibrosis Bronchiectasis; HRCT, High-Resolution Computed Tomography; BSI, Bronchiectasis Severity Index; ERS, European Respiratory Society; BTS, British Thoracic Society; MDR, Multidrug Resistant; MDR-GNB, Multidrug-Resistant Gram-Negative Bacteria; PA, *Pseudomonas aeruginosa*; NTM, Non-Tuberculous Mycobacteria; ABPA, Allergic Bronchopulmonary Aspergillosis; VAS, Visual Analog Scale; QOL-B, Quality of Life–Bronchiectasis Questionnaire; LCQ, Leicester Cough Questionnaire; MRC, Medical Research Council; SD, Standard Deviation; CI, Confidence Interval; χ^2, Chi-square test; df, Degrees of Freedom; *p*, Probability value; SPSS, Statistical Package for the Social Sciences; IRB, Institutional Review Board; IEC, Institutional Ethics Committee; FEV_1, Forced Expiratory Volume in the First Second; FVC, Forced Vital Capacity; CRP, C-Reactive Protein; IL-8, Interleukin-8; DNA, Deoxyribonucleic Acid; ROS, Reactive Oxygen Species; ATS, American Thoracic Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; AMK, Amikacin; ERD, Erdosteine; SC, Standard Care; ACT, Airway Clearance Therapy; AIR-BX, Aztreonam for Inhalation Solution in Bronchiectasis Trials; ORBIT, Oral Inhaled Colistin in Bronchiectasis Trial; RESPIRE, Randomized Evaluation of Safety and Efficacy of Ciprofloxacin in Respiratory Tract Infections and Exacerbations.

References

1. Chalmers, J.D.; Haworth, C.S.; Flume, P.; Long, M.B.; Burgel, P.-R.; Dimakou, K.; Blasi, F.; Herrero-Cortina, B.; Dhar, R.; Chotirmall, S.H.; et al. European Respiratory Society clinical practice guideline for the management of adult bronchiectasis. *Eur. Respir. J.* **2025**, *66*, 2501126. [CrossRef]
2. Polverino, E.; Goeminne, P.C.; McDonnell, M.J.; Aliberti, S.; Marshall, S.E.; Loebinger, M.R.; Murris, M.; Cantón, R.; Torres, A.; Dimakou, K.; et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur. Respir. J.* **2017**, *50*, 1700629. [CrossRef]
3. Hill, A.T.; Sullivan, A.L.; Chalmers, J.D.; De Soyza, A.; Elborn, S.J.; Floto, A.R.; Grillo, L.; Gruffydd-Jones, K.; Harvey, A.; Haworth, C.S.; et al. British Thoracic Society Guideline for bronchiectasis in adults. *Thorax* **2019**, *74*, 1–69. [CrossRef]
4. Chalmers, J.D.; Goeminne, P.; Aliberti, S.; McDonnell, M.J.; Lonni, S.; Davidson, J.; Poppelwell, L.; Salih, W.; Pesci, A.; Dupont, L.J.; et al. The Bronchiectasis Severity Index: An international derivation and validation study. *Am. J. Respir. Crit. Care Med.* **2014**, *189*, 576–585. [CrossRef]
5. Chalmers, J.D.; Chotirmall, S.H. Bronchiectasis: New therapies and new perspectives. *Lancet Respir. Med.* **2018**, *6*, 715–726. [CrossRef]
6. McCallion, P.; De Soyza, A. Cough and bronchiectasis. *Pulm. Pharmacol. Ther.* **2017**, *47*, 77–83. [CrossRef]
7. Dhar, R.; Singh, S.; Talwar, D.; Mohan, B.M.; Tripathi, S.K.; Swarnakar, R.; Trivedi, S.; Rajagopala, S.; D'Souza, G.; Padmanabhan, A.; et al. Clinical outcomes of bronchiectasis in India: Data from the EMBARC/Respiratory Research Network of India Registry. *Eur. Respir. J.* **2023**, *61*, 2200611. [CrossRef]
8. Cazzola, M.; Page, C.; Rogliani, P.; Calzetta, L.; Matera, M.G. Multifaceted beneficial effects of erdosteine: More than a mucolytic agent. *Drugs* **2020**, *80*, 1799–1809. [CrossRef]

9. Loebinger, M.R.; Polverino, E.; Blasi, F.; Elborn, J.C.; Chalmers, J.D.; Tiddens, H.A.W.M.; Goossens, H.; Tunney, M.; Zhou, W.; Angyalosi, G.; et al. Efficacy and safety of tobramycin inhalation powder in bronchiectasis patients with *Pseudomonas aeruginosa* infection: Design of the iBEST-1 study. *Pulm. Pharmacol. Ther.* **2019**, *58*, 101834. [CrossRef]
10. Reiff, D.B.; Wells, A.U.; Carr, D.H.; Cole, P.J.; Hansell, D.M. CT findings in bronchiectasis: Limited value in distinguishing between idiopathic and specific types. *AJR Am. J. Roentgenol.* **1995**, *165*, 261–267. [CrossRef] [PubMed]
11. Cazzola, M.; Rogliani, P.; Calzetta, L.; Hanania, N.A.; Matera, M.G. Impact of mucolytic agents on COPD exacerbations: A pairwise and network meta-analysis. *COPD J. Chronic Obstr. Pulm. Dis.* **2017**, *14*, 552–563. [CrossRef]
12. Brodt, A.M.; Stovold, E.; Zhang, L. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: A systematic review. *Ann. Am. Thorac. Soc.* **2014**, *11*, 382–393. [CrossRef] [PubMed]
13. Barker, A.F.; Couch, L.; Fiel, S.B.; Gotfried, M.H.; Ilowite, J.; Meyer, K.C.; O'DOnnell, A.; Sahn, S.A.; Smith, L.J.; Stewart, J.O.; et al. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. *Am. J. Respir. Crit. Care Med.* **2000**, *162*, 481–485. [CrossRef]
14. Haworth, C.S.; Foweraker, J.E.; Wilkinson, P.; Kenyon, R.F.; Bilton, D. Inhaled colistin in patients with bronchiec-tasis and chronic Pseudomonas aeruginosa infection. *Am. J. Respir. Crit. Care Med.* **2014**, *189*, 975–982. [CrossRef]
15. Barker, A.F.; O'Donnell, A.E.; Flume, P.; Thompson, P.J.; Ruzi, J.D.; De Gracia, J.; Boersma, W.G.; Soyza, A.D.; Shao, L.; Zhang, J.; et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): Two randomised double-blind placebo-controlled phase 3 trials. *Lancet Respir. Med.* **2014**, *2*, 738–749. [CrossRef]
16. De Soyza, A.; Aksamit, T.; Bandel, T.J.; Criollo, M.; Elborn, J.S.; Operschall, E.; Polverino, E.; Roth, K.; Winthrop, K.L.; Wilson, R. RESPIRE 1: A phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur. Respir. J.* **2018**, *51*, 1702052. [CrossRef] [PubMed]
17. Aksamit, T.R.; De Soyza, A.; Bandel, T.J.; Criollo, M.; Elborn, J.S.; Operschall, E.; Polverino, E.; Roth, K.; Winthrop, K.L.; Wilson, R. RESPIRE 2: A phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur. Respir. J.* **2018**, *51*, 1702053. [CrossRef]
18. Dal Negro, R.W.; Wedzicha, J.A.; Iversen, M.; Fontana, G.; Page, C.; Cicero, A.F.; Pozzi, E.; Calverley, P.M.A. Effect of erdosteine on the rate and duration of COPD exacerbations: The RESTORE study. *Eur. Respir. J.* **2017**, *50*, 1700711. [CrossRef]
19. Murray, M.P.; Turnbull, K.; MacQuarrie, S.; Pentland, J.L.; Hill, A.T. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. *Eur. Respir. J.* **2009**, *34*, 125–131. [CrossRef]
20. Flume, P.A.; Chalmers, J.D.; Olivier, K.N. Advances in bronchiectasis: Endotyping, genetics, microbiome, and disease heterogeneity. *Lancet* **2018**, *392*, 880–890. [CrossRef]
21. Altenburg, J.; de Graaff, C.S.; van der Werf, T.S.; Boersma, W.G. Immunomodulatory effects of macrolide antibiotics—Part 2: Advantages and disadvantages of long-term, low-dose macrolide therapy. *Respiration* **2011**, *81*, 75–87. [CrossRef]
22. Haworth, C.S.; Bilton, D.; Chalmers, J.D. Inhaled antibiotics for non-cystic fibrosis bronchiectasis. *Respiration* **2014**, *88*, 391–402. [CrossRef]
23. Chalmers, J.D.; Aliberti, S.; Filonenko, A.; Shteinberg, M.; Goeminne, P.C.; Hill, A.T.; Fardon, T.C.; Obradovic, D.; Gerlinger, C.; Sotgiu, G.; et al. Characterization of the "frequent exacerbator phenotype" in bronchiectasis. *Am. J. Respir. Crit. Care Med.* **2018**, *197*, 1410–1420. [CrossRef]
24. Finch, S.; McDonnell, M.J.; Abo-Leyah, H.; Aliberti, S.; Chalmers, J.D. A comprehensive analysis of the impact of Pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. *Ann. Am. Thorac. Soc.* **2015**, *12*, 1602–1611. [CrossRef]
25. Daley, C.L.; Iaccarino, J.M.; Lange, C.; Cambau, E.; Wallace, R.J., Jr.; Andrejak, C.; Böttger, E.C.; Brozek, J.; Griffith, D.E.; Guglielmetti, L.; et al. Treatment of nontuberculous mycobacterial pulmonary disease: An official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2020**, *71*, 905–913. [CrossRef]
26. Murray, M.P.; Pentland, J.L.; Turnbull, K.; MacQuarrie, S.; Hill, A.T. Sputum colour: A useful clinical tool in non-cystic fibrosis bronchiectasis. *Eur. Respir. J.* **2009**, *34*, 361–364. [CrossRef]
27. Bush, A.; Floto, R.A. Pathophysiology, causes and genetics of paediatric and adult bronchiectasis. *Respirology* **2019**, *24*, 1053–1062. [CrossRef]
28. Zhang, J.; Wang, S.; Shao, C. Reversible bronchial dilatation in adults. *Clin. Exp. Pharmacol. Physiol.* **2021**, *48*, 966–970. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.