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Reducing exacerbations with long-term inhaled amikacin for effective flare prevention (RELIEF study): A prospective comparative two-center, 52-week follow-up study in recurrent bronchiectasis

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ABSTRACT

Background: Recurrent exacerbations are the principal determinants of disease progression, hospitalization, healthcare utilization, and mortality in non-cystic fibrosis (CF) bronchiectasis. Although long-term inhaled antibiotics reduce exacerbations, the high cost of currently available agents limits their use in resource-limited settings. The reducing exacerbations with long-term inhaled amikacin for effective flare prevention (RELIEF) study evaluated the effectiveness and safety of long-term culture-guided nebulized amikacin in preventing recurrent bronchiectasis exacerbations.

Method: This prospective, comparative, two-center observational study included 144 adults hospitalized with acute exacerbation of high-resolution computed tomography (HRCT)-confirmed non-CF bronchiectasis, ≥ 3 exacerbations during the previous year, modified Reiff score > 10, and sputum cultures demonstrating resistant bacterial infection, predominantly multidrug-resistant Gram-negative organisms. Treatment allocation was determined by the treating physician; 72 patients received standard care plus culture-guided nebulized amikacin and 72 received standard care alone, with all participants followed for 52 weeks. Clinical outcomes included hospitalization duration, exacerbation frequency and severity, exacerbation duration, time to first exacerbation, exacerbation-free days, microbiological profile, antimicrobial resistance, and treatment-related adverse events.

Results: Nebulized amikacin significantly reduced hospitalization duration compared with standard care (7.48 ± 1.02 vs 12.50 ± 1.09 days; $p < 0.0001$). Severe exacerbations were markedly lower in the amikacin group (8 vs 26 episodes; $p < 0.00012$). Exacerbation duration decreased by 29.6%, 38.7%, and 40.1% for mild, moderate, and severe episodes, respectively (all $p < 0.0001$). Mean time to first exacerbation increased by 29.13%, 24.16%, and 17.78%, while exacerbation-free days improved by 17.71%, 27.33%, and 46.22%, respectively. *Pseudomonas aeruginosa* was the predominant pathogen (45.13%), with antimicrobial resistance in 64.61% of isolates. No nephrotoxicity or other significant systemic adverse events were observed throughout follow-up.

Conclusions: Long-term culture-guided nebulized amikacin was associated with reduced hospitalization duration, exacerbation burden, and recovery time while prolonging time to first exacerbation in this high-risk population. These findings support further evaluation of culture-guided nebulized amikacin as an adjunctive preventive strategy for carefully selected patients with recurrent non-CF bronchiectasis and resistant bacterial airway infection, particularly in resource-limited healthcare settings. Formal pharmacoeconomic evaluation is required before conclusions regarding cost-effectiveness can be made.

Keywords: bronchiectasis, RELIEF study, amikacin, nebulization, recurrent exacerbation, HRCT thorax, sputum culture DST

INTRODUCTION

Bronchiectasis is a chronic, progressive airway disease characterized by irreversible bronchial dilatation, persistent airway inflammation, impaired mucociliary clearance, recurrent bacterial infection, and repeated exacerbations. The disease follows a self-perpetuating "vicious vortex" in which chronic infection promotes airway inflammation, leading to structural lung damage, further bacterial colonization, and progressive decline in lung function. Frequent exacerbations are associated with accelerated disease progression, reduced quality of life, increased hospitalization, higher healthcare costs, and increased mortality. Therefore, preventing recurrent exacerbations has become a major therapeutic goal in bronchiectasis management [1-3].

Chronic colonization with Gram-negative organisms, particularly *Pseudomonas aeruginosa* (*P. aeruginosa*), is one of the strongest predictors of recurrent exacerbations, rapid lung function decline, and poor clinical outcomes. International

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guidelines recommend long-term inhaled antibiotics for patients with frequent exacerbations and chronic *P. aeruginosa* infection because inhaled therapy delivers high local antibiotic concentrations while minimizing systemic toxicity. Among available inhaled antibiotics, tobramycin, colistin, aztreonam, and gentamicin have demonstrated varying degrees of efficacy in reducing bacterial load and exacerbation frequency [4-6].

However, inhaled tobramycin remains expensive and is not readily affordable in many low- and middle-income countries, including India. Moreover, increasing antimicrobial resistance necessitates exploration of alternative, potentially affordable inhaled antibiotic strategies. Nebulized amikacin possesses excellent activity against many multidrug-resistant (MDR) Gram-negative pathogens, achieves high airway concentrations, and has shown encouraging results in small clinical studies and observational reports with acceptable safety profiles. Nevertheless, robust long-term data evaluating its effectiveness in preventing recurrent bronchiectasis exacerbations remain limited, particularly in resource-constrained settings [7-9].

The present reducing exacerbations with long-term inhaled amikacin for effective flare prevention (RELIEF) study was therefore designed as a prospective 52-week follow-up study to evaluate whether long-term nebulized amikacin, when added to standard care, reduces exacerbation frequency, prolongs time to first exacerbation, shortens recovery time, increases exacerbation-free days, and demonstrates acceptable safety among patients with recurrent bronchiectasis caused predominantly by drug-resistant Gram-negative bacterial infection.

METHOD

Data Source

The RELIEF study utilized prospectively collected clinical data from consecutive adult patients admitted with acute exacerbation of high-resolution computed tomography (HRCT)-confirmed non-cystic fibrosis (CF) bronchiectasis at Venkatesh Chest Hospital and MIMSR Medical College, Latur, Maharashtra, India. Patient recruitment was conducted between January 2023 and December 2024. A total of 144 eligible patients were enrolled after screening according to predefined inclusion and exclusion criteria. Clinical information, including demographic characteristics, comorbidities, HRCT findings (modified Reiff score), sputum microbiology with antimicrobial susceptibility testing, spirometry, Medical Research Council dyspnea score, exacerbation characteristics, hospitalization duration, and treatment-related adverse events, 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:02/2023, dated 03 January 2023, Clinical trial number: not applicable). Written informed consent was obtained from all participants before enrolment.

Treatment Allocation and Intervention

No random allocation was used. After eligibility assessment and consent, the treating physician determined whether a patient would receive adjunctive nebulized amikacin or standard care alone, based on the clinical and microbiological context and suitability for inhaled therapy. Seventy-two patients received standard care plus culture-guided nebulized amikacin, and 72 received standard care alone. In the amikacin group, nebulized amikacin was administered at 250 mg every 12 hours during the acute exacerbation and 250 mg every 24 hours as maintenance therapy for the planned 52-week follow-up. Standard care included airway-clearance therapy, antibiotics for acute exacerbations according to clinical and microbiological indications, and treatment of relevant comorbidities. The comparison group received standard care without long-term inhaled antibiotic therapy. Because treatment was physician-directed, the two groups were considered comparative observational cohorts, and observed between-group differences were interpreted as associations rather than definitive causal treatment effects.

Study Design

The RELIEF study was a prospective, comparative, two-center observational study. Consecutive eligible adults hospitalized with acute exacerbation of HRCT-confirmed non-CF bronchiectasis were screened according to predefined inclusion and exclusion criteria. Following eligibility assessment and written informed consent, treatment was allocated according to the treating physician's clinical judgment and the patient's microbiological and therapeutic profile. Seventy-two patients received standard care plus culture-guided nebulized amikacin and 72 received standard care alone. All participants were followed prospectively for 52 weeks. The study was therefore analyzed as a comparative observational cohort study rather than as a randomized controlled trial.

Study Objectives

Primary objective

To evaluate the association between long-term culture-guided nebulized amikacin, used as an adjunct to standard care, and recurrent exacerbation outcomes in adults with severe non-CF bronchiectasis and resistant bacterial infection over a 52-week follow-up period.

Secondary objectives

1. To compare the duration of hospitalization during the index exacerbation between patients receiving nebulized amikacin plus standard care and those receiving standard care alone.
2. To compare the frequency and severity of bronchiectasis exacerbations between the two treatment groups during follow-up.
3. To compare the duration of exacerbations (time to clinical recovery) between the two treatment groups.
4. To compare the time to first exacerbation during follow-up between the two treatment groups.
5. To compare the number of exacerbation-free days over 52 weeks between the two treatment groups.
6. To evaluate the safety profile of long-term inhaled amikacin through serial clinical assessment and renal function monitoring.
7. To describe the microbiological spectrum and antimicrobial resistance profile of predominant pathogens isolated from sputum cultures in recurrent bronchiectasis.

8. To describe the feasibility of long-term inhaled amikacin as a therapeutic strategy in a resource-limited healthcare setting; formal pharmacoeconomic evaluation was not performed.

Inclusion Criteria

Patients were enrolled if they fulfilled all of the following criteria:

1. Age ≥ 18 years.
2. HRCT-confirmed bronchiectasis.
3. History of ≥3 documented exacerbations requiring antibiotic treatment and/or hospitalization during the preceding 12 months.
4. Hospitalization for an acute exacerbation at the time of enrolment.
5. Modified Reiff Score >10 on HRCT thorax, indicating severe radiological disease.
6. Positive sputum microbiological culture demonstrating predominant bacterial infection with antimicrobial susceptibility testing (drug susceptibility testing [DST]) showing resistance to commonly prescribed antibiotics.
7. Isolation of one of the following organisms:
   - *P. aeruginosa*
   - *Acinetobacter spp.*
   - *Klebsiella pneumoniae*
   - *Escherichia coli*
   - *Staphylococcus aureus*
8. Ability to perform nebulization therapy and comply with 52-week follow-up.

Exclusion Criteria

Patients were excluded if they had any of the following:

1. Age < 18 years.
2. CF-associated bronchiectasis.
3. Active pulmonary tuberculosis or nontuberculous mycobacterial lung disease.
4. Active allergic bronchopulmonary aspergillosis.
5. Severe renal impairment (or contraindication to aminoglycoside therapy).
6. Known hypersensitivity to amikacin or other aminoglycosides.
7. Pregnancy or lactation.
8. Inability to complete follow-up or refusal to provide informed consent.
9. Sputum culture demonstrating predominant *Streptococcus pneumoniae* or *Haemophiles influenzae*, as these organisms were excluded from the study because long-term inhaled aminoglycoside therapy is primarily intended for chronic infections caused by resistant Gram-negative pathogens.
10. Mixed infections in which *S. pneumoniae* or *H. influenzae* were the predominant isolates.

Rationale For Long-Term Use of Nebulized Amikacin

Recurrent exacerbations in bronchiectasis are associated with persistent airway colonization with resistant bacteria, particularly *P. aeruginosa*, resulting in chronic inflammation, progressive lung damage, repeated hospitalizations, and impaired quality of life. Long-term inhaled antibiotic therapy delivers high local antimicrobial concentrations directly to the airways while minimizing systemic exposure and toxicity. Although inhaled antibiotics such as tobramycin are effective, their high cost and limited availability restrict their use in many resource-limited settings. Amikacin possesses broad-spectrum activity against several resistant Gram-negative pathogens and can be administered by nebulization. Therefore, this study evaluated the association of long-term culture-guided nebulized amikacin with exacerbation frequency and severity, exacerbation-free intervals, recovery time, and safety in carefully selected patients with recurrent non-CF bronchiectasis. Formal pharmacoeconomic evaluation was not performed.

METHODOLOGY

The overall methodology of the RELIEF study is summarized in **Figure 1**. Briefly, this was a prospective, comparative, two-center observational study conducted in adults hospitalized with acute exacerbation of HRCT-confirmed non-CF bronchiectasis. After screening according to predefined inclusion and exclusion criteria and obtaining written informed consent, eligible patients were allocated by the treating physician to either long-term culture-guided nebulized amikacin plus standard care or standard care alone. Patients were followed prospectively for 52 weeks with scheduled clinical assessments, including four-weekly renal function monitoring in the amikacin group. During follow-up, hospitalization duration, exacerbation frequency and severity, duration of exacerbations, time to first exacerbation, exacerbation-free days, sputum microbiological findings with antimicrobial susceptibility testing, and treatment-related adverse events were prospectively recorded and analyzed. Because allocation was not randomized, potential confounding and selection bias were considered when interpreting between-group comparisons. The complete study workflow is illustrated in **Figure 1**.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean (M) ± standard deviation (SD), whereas categorical variables were summarized as frequencies and percentages. Baseline demographic characteristics were described and compared between treatment groups to assess the distribution of measured baseline characteristics. Continuous outcome variables—including hospitalization duration, duration of exacerbation, time to first exacerbation, and exacerbation-free days—were compared using the independent-samples Student's t-test (unpaired t-test) after confirming approximate normality of data distribution. Mean differences between groups were reported together with their 95% confidence intervals (CIs). Categorical variables, including the distribution of mild, moderate, and severe exacerbations, were analyzed using the Pearson Chi-square (χ^2) test. Two-sided statistical testing was employed throughout the analysis, and a p-value < 0.05 was considered statistically significant. No interim analyses were performed. All participants with available follow-up data were analyzed according to the treatment group to which they were clinically allocated. Missing outcome

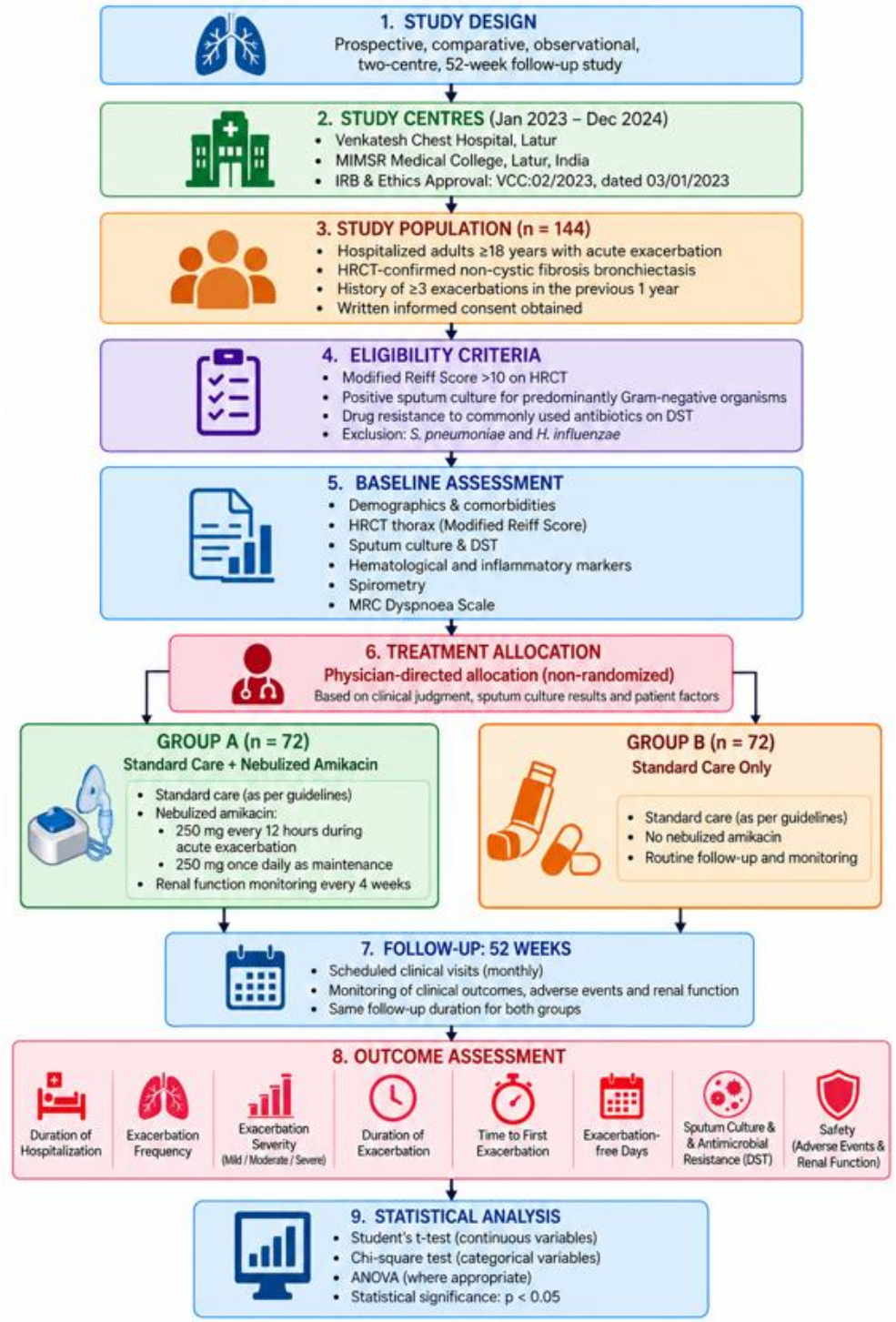


Figure 1. Methodology of RELIEF study (revised to reflect physician-directed allocation and physician-directed allocation) (the authors' own work)

data were minimal and therefore no imputation procedures were required. Given the non-randomized observational design, statistical comparisons were interpreted as associations and no causal effect was inferred.

RESULTS

Age and gender distribution in amikacin nebulization plus standard care group (n = 72) and standard care group (n = 72) were 50.88 years (23-70 years) and 49.68 years (21-72 years), respectively; males 45.83% (33/72) and females 54.16% (39/72), and males 48.61% (35/72) and females 51.38% (37/72), respectively (**Table 1**).

Duration of hospitalization in acute exacerbation in indoor setting during enrolment in amikacin nebulization plus standard care group (n = 72) was 7.48 ± 1.02 days and 12.50 ± 1.09 days in standard care group (n = 72) ($p < 0.0001$) (**Table 2**).

Sputum microbiological workup with culture and DST, pseudomonas species in 45.13% (65/144) cases and resistance in 64.61% (42/65) cases, Acinetobacter species in 18.75% (27/144) cases and resistance in 74.07% (20/27) cases,

Table 1. Baseline demographic characteristics of the study population

Characteristic	Standard care plus amikacin nebulization (n = 72)	Standard care only (n = 72)
Mean age: Years	50.88	49.68
Age range: Years	23-70	21-72
Male: n (%)	33 (45.83)	35 (48.61)
Female: n (%)	39 (54.17)	37 (51.39)

Table 2. Duration of therapy in both the groups

Outcome	Standard care plus amikacin nebulization (n = 72): M ± SD	Standard care only (n = 72): M ± SD	p-value; mean difference (95% CI)
Hospitalization duration during index exacerbation (days), n = 144	7.48 ± 1.02 (n = 72)	12.50 ± 1.09 (n = 72)	p < 0.0001; 5.02 days (95% CI 4.66-5.37); 50.20% relative difference

Table 3. Predominant microbiological profile and antimicrobial resistance pattern

Pathogen	Number of cases (n = 144) (%)	Antibiotic resistance (%)
P. aeruginosa	65 (45.13)	42 (64.61)
Acinetobacter	27 (18.75)	20 (74.07)
Staphylococcus aureus	21 (14.58)	12 (57.14)
Klebsiella pneumoniae	26 (18.05)	19 (73.07)
Escherichia coli	5 (3.47)	2 (40.00)

Table 4. Exacerbation episodes in the two treatment groups during 52-week follow-up

	Standard care plus amikacin nebulization (n = 72)	Standard care only (n = 72)
Bronchiectasis exacerbation mild (n = 43)	31	12
Bronchiectasis exacerbation moderate (n = 45)	22	23
Bronchiectasis exacerbation severe (n = 34)	8	26

Note. $\chi^2 = 17.97$; $p < 0.00012$

Table 5. Duration of exacerbations in the two treatment groups

	Standard care plus amikacin nebulization (n = 72): M ± SD	Standard care only (n = 72): M ± SD	p-value
Bronchiectasis exacerbation mild (n = 43)	4.548 ± 1.060 days (n = 31)	7.500 ± 0.520 days (n = 12)	p < 0.0001n(95% CI 2.30 to 3.60) 29.60% difference
Bronchiectasis exacerbation moderate (n = 45)	7.045 ± 1.290 days (n = 22)	10.913 ± 1.470 days (n = 23)	p < 0.0001 (95% CI 3.03 to 4.70) 38.70% difference
Bronchiectasis exacerbation severe (n = 34)	8.175 ± 1.387 days (n = 8)	12.384 ± 1.090 days (n = 26)	p < 0.0001 (95% CI 3.08 to 4.92) 40.10% difference

Klebsiella species in 18.05% (26/144) and resistance in 73.07% (19/26) cases, Staphylococcus species in 14.58% (21/144) cases and resistance in 57.14% (12/21) cases and *Escherichia coli* in 3.47% (5/144) cases and resistance in 40% (2/5) cases (**Table 3**).

During follow-up, exacerbation frequencies with severity (FACED/BSI core) as mild (n = 43), moderate (n = 45) and severe (n = 34) were 31, 22 and 8 episodes, respectively in amikacin nebulization plus standard care group and 12, 23 and 26 episodes, respectively in standard care group ($p < 0.00012$) (**Table 4**).

Exacerbation duration of mild category in both the groups was 4.54 ± 1.05 days versus 7.5 ± 0.52 days ($p < 0.0001$), moderate category in both the groups were 7.04 ± 1.29 days versus 10.91 ± 1.47 days ($p < 0.0001$) and severe category in both the groups were 8.17 ± 1.38 days versus 12.38 ± 1.09 days ($p < 0.0001$) (**Table 5**).

Mean time to exacerbation in mild category in both the groups were 97.38 ± 12.87 days versus 68.25 ± 10.36 days ($p < 0.0001$), moderate category in both the groups were 97.81 ± 9.31 days versus 73.65 ± 13.86 days ($p < 0.0001$) and severe category in both the groups were 95.5 ± 10.87 days versus 77.72 ± 12.07 days ($p < 0.0008$). Difference in mean time to exacerbation in both groups were 29.13% in mild, 24.16% in moderate and 17.78% in severe category (**Table 6**).

Exacerbation free days in mild category in both the groups were 96.4 ± 11.24 days versus 78.33 ± 10.79 days ($p < 0.0001$), moderate category in both the groups were 108.59 ± 9.34 days versus 81.26 ± 10.66 days ($p < 0.0001$) and severe category in both the groups were 122.25 ± 10.66 days versus 76.03 ± 10.29 days ($p < 0.0001$). Difference in exacerbation free days in both groups were 17.71% in mild, 27.33% in moderate and 46.22% in severe category. No systemic or real function related adverse events documented in present study (**Table 7**).

DISCUSSION

Covariates Analysis of Present Study

The present RELIEF study evaluated the association of long-term nebulized amikacin with clinical outcomes in patients with recurrent exacerbation bronchiectasis predominantly colonized with resistant bacterial pathogens. Baseline measured demographic characteristics were broadly similar between the treatment groups; however, because treatment allocation was physician-directed without random allocation, residual confounding and selection bias cannot be excluded. The mean age of patients in the nebulized amikacin plus standard care group was 50.88 years, while that of the

Table 6. Mean time to first exacerbation in the two treatment groups

	Standard care plus amikacin nebulization (n = 72): M ± SD	Standard care only (n = 72): M ± SD	p-value
Bronchiectasis exacerbation mild (n = 43)	97.38 ± 12.87 days (n = 31)	68.25 ± 10.36 days (n = 12)	p < 0.0001 (95% CI -37.54 to -20.72) 29.13% difference
Bronchiectasis exacerbation moderate (n = 45)	97.81 ± 9.31 days (n = 22)	73.65 ± 13.86 days (n = 23)	p < 0.0001 (95% CI -31.29 to -17.03) 24.16% difference
Bronchiectasis exacerbation severe (n = 34)	95.5 ± 10.87 days (n = 26)	77.72 ± 12.07 days (n = 8)	p < 0.0008 (95% CI -27.51 to -8.04) 17.78% difference

Table 7. Exacerbation-free days in the two treatment groups

	Standard care plus amikacin nebulization (n = 72): M ± SD	Standard care only (n = 72): M ± SD	p-value
Bronchiectasis exacerbation mild (n = 43)	96.40 ± 11.24 days (n = 31)	78.33 ± 10.79 days (n = 12)	p < 0.0001 (95% CI -25.34 to -10.07) 17.71% difference
Bronchiectasis exacerbation moderate (n = 45)	108.59 ± 9.34 days (n = 22)	81.26 ± 10.66 days (n = 23)	p < 0.0001 (95% CI -33.3664 to -21.2936) 27.33 % difference
Bronchiectasis exacerbation severe (n = 34)	122.25 ± 12.76 days (n = 8)	76.03 ± 10.29 days (n = 26)	p < 0.0001 (95% CI -55.17 to -37.26) 46.22% difference

standard care group was 49.68 years, with an overall age range of 21-72 years. Both groups demonstrated a nearly equal sex distribution, with a slight female predominance. Similar age distributions have been reported in the European multicenter bronchiectasis audit and research collaboration (EMBARC) registry and the Indian bronchiectasis registry, where bronchiectasis predominantly affects middle-aged and elderly adults with comparable sex representation [1, 2, 7, 8, 10]. These findings provide context for the characteristics of the study population but should not be interpreted as evidence that confounding was eliminated.

A major observation of the present study was the significant reduction in the duration of hospitalization during the index exacerbation among patients receiving nebulized amikacin. Patients treated with nebulized amikacin required a mean hospital stay of 7.48 ± 1.02 days compared with 12.50 ± 1.09 days in those receiving standard care alone ($p < 0.0001$). This reduction is clinically meaningful because prolonged hospitalization is associated with increased healthcare expenditure, greater risk of hospital-acquired infections, reduced quality of life, and accelerated disease progression [1, 3, 10]. Although previous randomized trials evaluating inhaled tobramycin, gentamicin, colistin, and ciprofloxacin have primarily demonstrated reductions in bacterial load and exacerbation frequency, limited evidence has specifically addressed hospitalization duration [4, 5, 9]. Therefore, the present findings extend existing evidence by demonstrating that adjunctive nebulized amikacin may facilitate earlier clinical recovery, shorten hospital stay, and reduce healthcare resource utilization. Furthermore, the considerably lower cost of amikacin compared with commercially available inhaled antibiotics makes this therapeutic strategy particularly attractive in low- and middle-income countries [2, 3, 9, 10].

Microbiological analysis demonstrated that *P. aeruginosa* remained the predominant pathogen, isolated in 45.13% of patients, with antimicrobial resistance documented in 64.61% of isolates. This observation closely parallels reports from EMBARC, the bronchiectasis research registry, and the Indian bronchiectasis registry, where chronic *P. aeruginosa* infection consistently predicts frequent exacerbations, accelerated lung function decline, increased hospitalization, and mortality [1, 2, 7, 8, 10, 11]. The high prevalence of MDR *P. aeruginosa* in the present study further emphasizes the need for inhaled antibiotic therapy capable of delivering high local drug concentrations directly to infected airways while minimizing systemic toxicity [2-5, 9, 10].

Besides *P. aeruginosa*, the present study identified substantial colonization with *Acinetobacter spp.* (18.75%), *Klebsiella pneumoniae* (18.05%), *Staphylococcus aureus* (14.58%), and *Escherichia coli* (3.47%). Importantly, antimicrobial resistance exceeded 70% among both Acinetobacter and Klebsiella isolates, highlighting the increasing burden of MDR Gram-negative organisms in patients with advanced bronchiectasis. These findings likely reflect repeated antibiotic exposure, recurrent hospital admissions, and chronic airway colonization. Current European Respiratory Society (ERS) and British Thoracic Society (BTS) guidelines strongly recommend routine sputum microbiological surveillance and antimicrobial susceptibility testing to individualize antibiotic selection, particularly in patients experiencing recurrent exacerbations caused by resistant Gram-negative pathogens [10-16]. Consequently, the microbiological profile observed in the present study provides a strong rationale for culture-directed long-term nebulized amikacin therapy in carefully selected patients with recurrent bronchiectasis.

Overall, the balanced baseline demographic characteristics together with the predominance of MDR Gram-negative pathogens provide a robust clinical framework for interpreting the superior outcomes observed with nebulized amikacin during long-term follow-up. The findings reinforce the importance of routine sputum microbiology, antimicrobial susceptibility testing, and pathogen-directed inhaled antibiotic therapy as key components of precision medicine for reducing exacerbation burden, preventing disease progression, and improving long-term clinical outcomes in bronchiectasis [3-5, 7, 9, 10].

Disease Outcome Defining Findings in Present Study

The principal finding of the present RELIEF study was that long-term nebulized amikacin significantly reduced the frequency, severity, and duration of exacerbations while prolonging the time to first exacerbation and increasing exacerbation-free days over a 52-week follow-up period. These findings support the concept that chronic bacterial colonization, particularly with MDR Gram-negative organisms, perpetuates the “vicious vortex” of bronchiectasis through persistent infection, neutrophilic inflammation, impaired

mucociliary clearance, and progressive airway destruction. Interrupting this cycle with targeted inhaled antibiotic therapy may substantially improve long-term clinical outcomes [1-3, 5, 6, 9].

During follow-up, patients receiving nebulized amikacin experienced markedly fewer moderate and severe exacerbations than those receiving standard care alone. Although mild exacerbations constituted the largest proportion of episodes in the amikacin group, only 8 severe exacerbations occurred compared with 26 severe exacerbations in the control group ($p < 0.00012$). This shift from severe to milder exacerbations is clinically important because severe exacerbations are associated with accelerated decline in lung function, increased hospital admissions, poorer quality of life, and higher mortality [1-3, 6, 9]. Similar reductions in exacerbation frequency have been demonstrated with inhaled tobramycin, gentamicin, colistin, aztreonam, ciprofloxacin dry powder, and liposomal ciprofloxacin in selected bronchiectasis populations [1, 2, 5, 11-13]. The present study extends these observations by demonstrating comparable clinical benefits with nebulized amikacin, a considerably more economical inhaled antibiotic that is particularly relevant for resource-limited healthcare settings.

An equally important observation was the significant reduction in exacerbation duration among patients receiving nebulized amikacin. Recovery from mild, moderate, and severe exacerbations was consistently faster than in patients receiving standard therapy alone, with reductions of approximately 29.6%, 38.7%, and 40.1%, respectively. Faster clinical recovery probably reflects rapid reduction in bacterial burden within the airways, attenuation of neutrophilic inflammation, improved mucus clearance, and earlier restoration of airway function [1, 3, 6, 7]. Although previous inhaled antibiotic trials have mainly evaluated annual exacerbation rates, relatively few have demonstrated substantial shortening of exacerbation duration [4-6]. Therefore, the present findings add clinically meaningful evidence supporting inhaled amikacin as an adjunctive treatment capable of accelerating recovery during exacerbation episodes.

Another major strength of the RELIEF study is the demonstration that nebulized amikacin significantly prolonged the mean time to first exacerbation. Patients receiving inhaled amikacin remained clinically stable for nearly three months before developing another exacerbation, significantly longer than those receiving standard care. The percentage improvement in time to exacerbation reached 29.13% in mild disease, 24.16% in moderate disease, and 17.78% in severe disease, indicating sustained suppression of bacterial colonization throughout follow-up. Time to first exacerbation is increasingly recognized as an important endpoint because it reflects long-term disease stability and predicts future healthcare utilization [1, 5, 6, 9, 13, 14]. Previous phase III trials evaluating inhaled ciprofloxacin and observational studies of inhaled gentamicin similarly demonstrated delayed recurrence of exacerbations, supporting the present findings [11, 13, 14].

The study further demonstrated a significant increase in exacerbation-free days, with improvements of 17.71%, 27.33%, and 46.22% in mild, moderate, and severe disease categories, respectively. This finding has considerable clinical importance because exacerbation-free days directly reflect patient wellbeing, symptom control, daily activity, work productivity, and quality of life [1-3, 6, 9]. Prolonged periods without exacerbations also reduce cumulative antibiotic exposure, minimize hospitalization, decrease healthcare costs, and potentially slow structural progression of bronchiectasis [2, 3, 5, 6, 9]. The marked improvement observed in patients with severe disease suggests that individuals with recurrent MDR Gram-negative infection may derive the greatest benefit from long-term inhaled amikacin therapy.

An additional reassuring finding was the excellent safety profile of long-term nebulized amikacin. No systemic toxicity, nephrotoxicity, or treatment-related serious adverse events were observed during the 52-week follow-up, despite regular administration of an aminoglycoside. Renal function monitoring every four weeks remained stable throughout the study. These observations are biologically plausible because inhaled delivery achieves high antimicrobial concentrations within the bronchial tree while maintaining minimal systemic absorption [4, 5, 11]. Previous studies evaluating inhaled aminoglycosides have similarly demonstrated low serum drug concentrations and substantially reduced risks of nephrotoxicity and ototoxicity compared with intravenous administration [4, 5, 11]. The present study therefore provides additional long-term safety evidence supporting nebulized amikacin as a practical maintenance therapy for selected patients with recurrent bronchiectasis.

Taken together, the present findings indicate that culture-directed long-term nebulized amikacin was associated with lower exacerbation frequency and severity, shorter recovery time, longer time to first exacerbation, and more exacerbation-free days. Considering its lower cost compared with some currently available inhaled antibiotics, nebulized amikacin may represent a practical option for carefully selected patients in resource-limited settings. However, the observational design precludes definitive attribution of these differences to amikacin alone, and formal pharmacoeconomic evaluation was not performed [1-6, 9].

Drug Susceptibility Testing Pattern and Clinical Implications

An important additional finding of the present RELIEF study was the high prevalence of antimicrobial resistance among the isolated bacterial pathogens. DST demonstrated that the majority of *P. aeruginosa* (64.61%), *Acinetobacter spp.* (74.07%), *Klebsiella pneumoniae* (73.07%), and *Staphylococcus aureus* (57.14%) isolates were resistant to commonly prescribed antibiotics, while 40% of *Escherichia coli* isolates also exhibited antimicrobial resistance. These findings indicate a substantial burden of MDR organisms among patients with recurrent bronchiectasis and likely reflect repeated antibiotic exposure, recurrent hospitalizations, and chronic airway colonization. Similar trends of increasing antimicrobial resistance among Gram-negative pathogens have been reported in international bronchiectasis registries and observational studies, particularly among patients with frequent exacerbations and chronic *P. aeruginosa* infection [1-3, 8, 10].

The observed DST pattern provides a strong microbiological rationale for the use of culture-guided nebulized amikacin in the present study. Conventional systemic antibiotics frequently fail to achieve adequate airway concentrations in chronically colonized bronchi, whereas inhaled amikacin delivers high local drug concentrations directly to the site of infection while minimizing systemic

exposure. This pharmacokinetic advantage may overcome intermediate antimicrobial resistance and suppress bacterial biofilm formation, thereby reducing bacterial burden and recurrent exacerbations [2, 4, 5, 7, 9, 10].

Furthermore, current ERS and BTS guidelines strongly recommend obtaining sputum culture and antimicrobial susceptibility testing before initiating long-term inhaled antibiotic therapy, particularly in patients with recurrent exacerbations caused by resistant Gram-negative organisms [2, 3, 16]. The present findings reinforce this recommendation and support precision medicine, whereby inhaled antibiotic selection is individualized according to microbiological profile and DST results rather than empirical antibiotic use. Such an approach not only improves clinical outcomes but also promotes antimicrobial stewardship by reducing inappropriate antibiotic exposure and limiting the emergence of further resistance [2, 3, 9, 10].

Limitations of the Present Study

The present study has several limitations that should be considered while interpreting the findings. First, treatment allocation was physician-directed without random allocation, introducing potential confounding by indication and selection bias; therefore, observed between-group differences cannot be interpreted as definitive causal treatment effects. Second, the study was performed at only two centers, which may limit generalizability to other populations and healthcare settings. Third, the sample size was relatively modest, and larger multicenter prospective comparative studies or randomized controlled trials are required to validate these findings. Fourth, the 52-week follow-up, although adequate to assess recurrent exacerbations, does not provide information regarding very long-term outcomes such as lung function decline, radiological progression, or survival. Fifth, patient-reported outcomes, including health-related quality of life, symptom scores, cough severity, and treatment adherence, were not systematically evaluated. Sixth, serial microbiological eradication rates, bacterial load quantification, and emergence of amikacin-resistant organisms during long-term therapy were not assessed. Finally, although nebulized amikacin demonstrated an excellent observed safety profile with regular renal monitoring, formal audiometric evaluation for ototoxicity and pharmacoeconomic evaluation were not performed. These limitations should be considered when interpreting the reported associations.

Novel Findings of the Present Study

The RELIEF study provides several clinically relevant observations that add to the evidence on long-term inhaled antibiotic therapy in non-CF bronchiectasis. Unlike previous studies that primarily focused on inhaled tobramycin, colistin, or ciprofloxacin, the present study evaluated culture-guided long-term nebulized amikacin in patients with recurrent exacerbations and resistant bacterial infection over a 52-week follow-up. Nebulized amikacin was associated with shorter hospitalization duration, lower frequency and severity of exacerbations, shorter recovery time, longer time to first exacerbation, and more exacerbation-free days, while no significant systemic adverse events were observed. Because treatment allocation was not randomized, these findings should be regarded as comparative associations requiring confirmation in adequately controlled studies.

A notable observation of this study was the apparent shift toward fewer severe exacerbations among patients receiving nebulized amikacin. Patients receiving nebulized amikacin had a longer mean time to first exacerbation, more exacerbation-free days, and shorter recovery times across exacerbation-severity categories. These clinically relevant differences extend beyond conventional endpoints reported in some inhaled antibiotic studies, but their causal relationship to amikacin cannot be established from this observational design.

Another important strength is the culture-guided treatment approach, whereby long-term inhaled amikacin was administered to selected patients with HRCT-confirmed severe bronchiectasis and sputum cultures demonstrating resistant bacterial infection. This targeted strategy supports individualized therapy based on microbiological profile and antimicrobial susceptibility testing rather than empirical antibiotic use, while also aligning with antimicrobial stewardship principles.

Importantly, despite prolonged aminoglycoside therapy, no nephrotoxicity or other significant systemic adverse events were observed during the 52-week follow-up with regular renal monitoring. These findings support the observed tolerability of nebulized amikacin in this selected cohort. However, formal audiometric and pharmacoeconomic assessments were not performed, and the observational design does not permit definitive comparison of safety or cost-effectiveness with alternative inhaled antibiotics.

CONCLUSIONS

In this selected population with recurrent non-CF bronchiectasis and resistant bacterial airway infection, long-term culture-guided nebulized amikacin was associated with shorter hospitalization duration and recovery time, fewer severe exacerbations, longer time to first exacerbation, and more exacerbation-free days over 52 weeks. Nebulized amikacin was well tolerated in this cohort, with no observed nephrotoxicity or other significant systemic adverse events during follow-up. Because treatment allocation was physician-directed and the study was observational, these findings should be interpreted as associations rather than definitive evidence of causality. Formal pharmacoeconomic and adequately powered controlled studies are warranted before conclusions regarding cost-effectiveness or broader clinical adoption can be made.

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AI statement: AI tools used solely for spelling, grammar, and general editing and methodology colour diagram preparation.

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