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Short-term Tolerance to Inhaled Antibiotics in Patients With Bronchial Infection not Associated With Cystic Fibrosis

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ABSTRACT

Introduction: The use of intravenous antibiotic formulations delivered by inhalation is controversial. Tolerance can be an issue and some treatment guidelines discourage this route of administration if the same antibiotic is available in an inhalation formulation.
Material and methods: This was a retrospective, observational, single-center study comparing tolerance to three antibiotics delivered by nebulization (intravenous formulations of ampicillin and gentamicin, and an inhalation formulation of colistimethate sodium) in patients with bronchial infection (BI), chronic bronchial infection (CBI), and/or recurrent respiratory infections. The study also aimed to identify factors potentially associated with tolerability.
Results: A total of 330 antibiotic tolerance tests were performed in 135 patients (mean age 68 years; 48.9% female; mean post-bronchodilator FEV_1% predicted 65.9%). Of these patients, 62.2% had bronchiectasis and 39.3% had chronic obstructive pulmonary disease (COPD). The best tolerated antibiotic was colistimethate. Overall, 89.6% of colistimethate doses were tolerated, compared to 69.5% of inhaled gentamicin doses ($P<0.001$) and 69.1% of ampicillin doses ($P<0.001$). Compared with colistimethate administration, the odds of intolerance were 5.69 times higher for gentamicin ($P<0.001$) and 6.21 times higher for ampicillin ($P<0.001$). In the univariate analysis, factors that may have been associated with antibiotic intolerance included smoking habit, worse post-bronchodilator FEV_1% predicted and a diagnosis of COPD. In the multivariate analysis, after adjustment for antibiotic type, smoking habit, post-bronchodilator FEV_1 and COPD diagnosis, the only factor influencing tolerance was the type of antibiotic used.
Conclusion: In patients with BI and/or CBI and/or recurrent respiratory infections, inhaled sodium colistimethate is significantly better tolerated than intravenous formulations of gentamicin and ampicillin for the inhalation route. The only factor influencing tolerance is the type of antibiotic used.

Tolerancia a corto plazo a antibióticos inhalados en pacientes con infección bronquial no debida a fibrosis quística

Palabras clave:
Tolerancia a antibióticos inhalados
Antibióticos inhalados
Antibióticos nebulizados
Infección bronquial crónica
Bronquiectasias

RESUMEN

Introducción: La utilización de formulaciones de antibióticos por vía inhalada es controvertida. Algunas normativas desaconsejan su empleo si el mismo antibiótico está disponible en formulaciones específicas para inhalación.
Material y métodos: Estudio retrospectivo, observacional y unicéntrico en pacientes sometidos a pruebas de tolerancia a tres antibióticos inhalados. Se comparó la tolerancia a la ampicilina, la gentamicina y el

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colistimetato sódico inhalados en pacientes con infección bronquial (IB) y/o infección bronquial crónica (IBC) y/o infecciones respiratorias recurrentes. Además, el estudio pretendía identificar los factores potencialmente asociados a la tolerabilidad.

Resultados: Se realizaron 330 pruebas de tolerancia a los antibióticos en 135 pacientes (edad media: 68 años; 48,9% mujeres; media del FEV_1 postbroncodilatador % predicho = 65,9%). El 62,2% de los pacientes tenían bronquiectasias, y el 39,3%, enfermedad pulmonar obstructiva crónica (EPOC). El antibiótico mejor tolerado fue el colistimetato. Se toleraron el 89,6% de las dosis de colistimetato, en comparación con el 69,5% de las de gentamicina inhalada ($p < 0,001$) y el 69,1% de las de ampicilina ($p < 0,001$). La probabilidad de no tolerar gentamicina y ampicilina fue, respectivamente, 5,69 y 6,21 veces mayor que la probabilidad de tolerar colistimetato ($p < 0,001$). En el análisis univariante, los factores que se asociaron con intolerancia a los antibióticos fueron el hábito tabáquico, un peor FEV_1 postbroncodilatador % predicho y el diagnóstico de EPOC. En el análisis multivariante, tras ajustar por tipo de antibiótico, hábito tabáquico, FEV_1 postbroncodilatador y diagnóstico de EPOC, el único factor que influyó en la tolerancia fue el tipo de antibiótico utilizado.

Conclusión: En pacientes con IB y/o IBC y/o infecciones respiratorias de repetición el colistimetato de sodio inhalado se tolera significativamente mejor que las formulaciones intravenosas de gentamicina y ampicilina empleadas por vía inhalada. El único factor que influye en la tolerancia es el tipo de antibiótico utilizado.

Introduction

The use of inhaled antibiotics is considered 'off-label' for the non-cystic fibrosis (CF) bronchiectasis population, given that most of supporting data was generated in the CF population. Nevertheless, a number of clinical practice guidelines recommend their use in patients with bronchiectasis or chronic obstructive pulmonary disease (COPD) and chronic bronchial infection (CBI) caused by potentially pathogenic microorganisms (PPM).[1,2] Numerous studies conducted in the non-CF population have demonstrated that the administration of inhaled antibiotics reduces PPM density, attenuates symptoms, and enhances health-related quality of life, while concurrently reducing the frequency of exacerbations and hospitalisations.[3–5] Patients with frequent disease exacerbations have worse quality of life, are more likely to be hospitalized, and have an increased risk of mortality.[6] However, only 50% of patients with bronchiectasis and frequent exacerbations have CBI, and only one third receives prophylactic antibiotic therapies.[6] A recent case report suggested that nebulized antibiotics can be an effective therapy in patients with recurrent respiratory infections without bronchiectasis, irrespective of the presence of bacterial pathogens in the lower respiratory tract.[7]

Targeted delivery of aerosolized antibiotics directly to the airways may have significant benefit with minimal side effects. The most common adverse events associated with inhaled antibiotics are bronchospasm, dyspnea, and cough, which occurred in 10%–30% of patients.[3–6] Most studies involving inhaled antibiotics withdrew patients who reported symptoms such as chest tightness, wheezing and shortness of breath, or who had a 10% or 15% reduction in forced expiratory volume in 1 second (FEV_1).[3,8] For this reason, current guidelines recommend a supervised test dose with pre- and post-spirometry to assess for bronchoconstriction and tolerability.[1,8,9] More than 95% of the inhaled antibiotics used in patients are specific inhalation formulations rather than intravenous antibiotic formulations delivered via inhalation.[10–12] The most commonly used intravenous antibiotic formulations administered via inhalation are gentamicin,[3] ceftazidime, and vancomycin.[10–12] Others, such as ampicillin, are used less frequently, although they have also been shown to be effective.[7,13,14]

Some consensus documents stipulate the use of parenteral antibiotic formulations administered via the nebulized route in exceptional cases, depending on the type of PPMs or their susceptibility to antibiotics.[3] Thus, Spanish Guidelines on the Treatment of Bronchiectasis in Adults advise against the use of intravenous formulations delivered via inhalation if the same antibiotic is available in a formulation for inhalation.[2] This recommendation is based on the assertion by some authors that intravenous formulations may be less well tolerated than specific inhalation formulations and confer an increased likelihood of adverse effects. However, other guidelines, including those of the British Thoracic Society for Bronchiectasis in Adults, recommend inhaled colistimethate as the first-line treatment in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection, while proposing nebulized gentamicin given as an alternative second-line treatment.[8] The discrepancy in the tolerability of inhaled antibiotics between the different studies may be attributed to the varying methodologies employed. For instance, some studies used bronchodilators prior to antibiotic administration, whereas others did not. Furthermore, different nebulizers have been used in diverse pathologies and severity levels, and the criteria for measuring tolerance vary widely.

The precise risk factors that may influence tolerance remain unclear, although several hypotheses have been postulated. These include gender, the type of inhaled antibiotic, bronchial hyperresponsiveness (BHR), and lower FEV_1.[1,15] Consequently, certain guidelines recommend that clinicians exercise extreme caution when treating patients with significant BHR or asthma and severely impaired lung function.[1,8,9]

This study was conducted to compare the tolerance of inhaled colistimethate, gentamicin and ampicillin in patients with BI and/or CBI and/or recurrent respiratory infections. We have also investigated the potential factors that may influence tolerance.

Material and methods

Study design and population

This was a retrospective, single-center study conducted in real-life conditions in adult patients undergoing routine tolerance testing to inhaled ampicillin, gentamicin and sodium colistimethate between March 2017 and December 2022. Patients presented with various chronic lung diseases, predominantly bronchiectasis and COPD, manifesting as BI and/or CBI and/or recurrent respiratory infections. The decision to perform tolerance testing to inhaled antibiotics was made based on the physician's judgment according to routine clinical practice.

We defined BI as persistent cough and mucopurulent or purulent sputum; CBI as the presence of two or more isolates of the

same organism at least 3 months apart in 1 year[9]; recurrent respiratory infections as three or more respiratory infections in the previous year; COPD as a post-bronchodilator FEV_1/forced vital capacity (FVC) of less than 0.7 in smokers or former smokers of at least 10 pack-years; BHR as a positive bronchodilatory response (an increase in FEV_1 of ≥12% and ≥200 ml following bronchodilator administration compared to baseline); and exacerbations as an increase in respiratory symptoms necessitating antibiotic treatment. Bronchiectasis was diagnosed by high-resolution computed tomography. The degree of dyspnea was assessed using the modified Medical Research Council (mMRC) dyspnea scale. We excluded patients unable to understand the protocol or to adequately perform spirometry or inhalation of antibiotics, those who had an exacerbation or hemoptysis in the 4 weeks prior to study inclusion, those allergic to any of the study antibiotics, and pregnant women.

The primary objective of the study was to assess the tolerability of ampicillin, gentamicin and sodium colistimethate in our patient cohort. The secondary objectives were to identify factors related to tolerance.

Protocol for nebulized antibiotic test dose

A standard inhaled antibiotic protocol was used for all patients in this study. Nebulizations were conducted in the laboratory of the Department of Pneumology. A vibrating mesh nebulizer (eFlow® rapid, PARI Pharma Iberia S.L., Madrid, Spain) with a mouthpiece was employed. The nebulizers and antibiotics were provided by the hospital. Patients were instructed and supervised by pulmonary function laboratory staff experienced in the correct and safe performance of nebulizations.

Baseline spirometry was conducted prior to starting the procedure. The patient was then bronchodilated to prevent bronchoconstriction (4 puffs of salbutamol and, in intolerant patients, 8 puffs of ipratropium bromide, with an inhalation chamber). Fifteen minutes after administering the bronchodilator, post-bronchodilator spirometry was performed. The antibiotic was nebulized immediately after the spirometry, and 15 min after nebulization of the antibiotic, the third spirometry (post-antibiotic spirometry) was performed. Oxygen saturation via pulse oximeter was also recorded prior to the intervention and after inhalation of the antibiotic. Each patient underwent tolerance tests on different days over a maximum period of 2 weeks. The order in which the tolerance tests were conducted was subject to variation, as the protocol was designed on the assumption that this factor did not exert an influence on tolerance.

The antibiotic formulations used were: (1) colistimethate sodium powder (Accord®, Accord Healthcare Laboratories, S.L.U., Barcelona, Spain) for intravenous and inhalatory use, reconstituted for nebulization by diluting 1 million IU of colistimethate sodium in 4 ml of 0.9% saline; (2) gentamicin sulfate (Genta Gobens®, Normon Laboratories, Madrid, Spain) for intravenous and intramuscular use, reconstituted for nebulization by diluting a 2 ml vial (40 mg gentamicin base/ml) in 2 ml of 0.9% saline; and (3) ampicillin powder (Gobemicina®, Normon Laboratories, Madrid, Spain) for intravenous and intramusculary use, reconstituted for nebulization by diluting 1 g of ampicillin sodium salt in 4 ml of 0.9% saline.

Measurements

In the baseline visit, we collected demographic and clinical information, exacerbations, microbiological isolates in sputum samples in the previous year, lung function parameters, oxygen saturation via pulse oximeter, and the subjective symptoms reported by the patient immediately after the antibiotic inhalation.

Tolerability criteria

The tolerability of inhaled antibiotics was assessed at each visit according to three parameters. A 6-item Likert-type questionnaire was administered to the patient to assess tolerability to the treatment within 15 min of inhaling the antibiotics. The questionnaire evaluated six items, namely chest tightness, dyspnea, wheezing, cough, pharyngeal irritation, and nausea/bad taste in the mouth. Responses to each question ranged from "0" (indicating no experience of the symptom in question) to "3" (indicating a high level of experience of the symptom in question). The patient was designated as intolerant, (1) if they answered "2" or "3" to any of the questions concerning chest tightness, dyspnea and wheezing, or if they answered "3" to any of the questions concerning cough, pharyngeal irritation and nausea/bad taste in the mouth; (2) if the mean post-bronchodilator FEV_1 decreased by at least 15% on post-antibiotic spirometry; or (3) at the discretion of the investigator (medical criteria), as some patients may not be able to adequately determine whether they have dyspnea and/or wheezing after inhaling the antibiotic, or may have a significant decrease in oxygen saturation.

Statistical analysis

Variables are presented as mean (standard deviation) for continuous variables, and as the absolute frequency and relative frequency for categorical variables. To evaluate the main objective, a univariable multilevel logistic model was fitted, where tolerance was the dependent variable, and the type of antibiotic was the independent variable. To adjust for the factors identified, the same modeling approach was used for factors that showed an effect with a *P*-value less than 0.10. In the multivariate analysis, effects with a *P*-value below 0.05 were considered significant.

We also examined the possibility that the relationship between antibiotics and tolerance was dependent on the presence of HRB or if it was affected by post-bronchodilator FEV_1%, categorized into levels from 0 to 29, 30 to 49, and above 50. To examine this relationship, models including the interaction between these variables and the type of antibiotic were fitted. A sensitivity analysis was conducted in which the study population was restricted to patients who had been tested for three antibiotics. All analyses were performed using STATA 18.0 software.

Ethical considerations

Patients were identified from the Spanish Computerized Registry of Patients with Bronchiectasis of the Hospital Ramón y Cajal, which is approved by the Clinical Research Ethics Committee of the hospital (reference number: 012/15).

Results

A total of 135 patients presenting with a range of chronic lung diseases underwent tolerance tests over the course of the study period. The patient cohort was 48.9% female with a mean age of 68.1 years (standard deviation [SD] 14.3), a post-bronchodilator FEV_1 of 65.9% (SD 25.3), and a post-antibiotic FEV_1 of 64.4% (SD 26.3). The most prevalent underlying lung conditions were bronchiectasis (62.5%) and COPD (39.3%). In total, 18 patients (13.3%) had BHR (Table 1). Of the 84 patients with bronchiectasis, 45 (53.6%) were classified as having mild disease, 25 (29.8%) moderate disease, and 14 (16.7%) severe disease, according to the FACED score.

Table 1
Baseline sociodemographic and clinical characteristics of the study population ($N = 135$).

Age, years	68.1 ± 14.3
Gender (% female)	66 (48.9%)
Smoking habits	
Never-smoker	57 (42.2%)
Former smoker	68 (50.4%)
Current smoker	10 (7.4%)
Smoking habit, packs/year (former smoker group)	44.1 ± 33.2
Smoking habit, packs/year (active smoker group)	31.4 ± 11.5
Microbiological characteristics	
CBI due to *Pseudomonas aeruginosa*	46 (34.1%)
Isolation of *Staphylococcus aureus*	13 (9.6%)
Isolation of *Stenotrophomonas maltophilia*	10 (7.4%)
Isolation of *Haemophilus influenzae*	5 (3.7%)
Isolation of other PPMs	13 (9.6%)
Presence of bronchiectasis	84 (62.2%)
Presence of COPD	53 (39.3%)
Presence of BHR	18 (13.3%)
Infectious exacerbations during the year before the tolerance tests	3.9 ± 3.2
Total number of tolerance tests performed	330
Number of tolerance tests performed on each patient	
1	15 (11.1%)
2	45 (33.3%)
3	75 (55.6%)
Post-bronchodilator FVC, % predicted	75.3 ± 21.1
Post-bronchodilator FEV_1, % predicted	65.9 ± 25.3
Post-antibiotic FVC% predicted	72.4 ± 22.4
Post-antibiotic FEV_1% predicted	64.4 ± 26.3

Values are expressed as means ± SD or as numbers (%).
BHR: bronchial hyperresponsiveness; CBI: chronic bronchial infection; COPD: chronic obstructive lung disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; PPM: potentially pathogenic microorganisms.

Tolerance to the inhaled antibiotics

A total of 330 tolerance tests were conducted on 135 patients. No fatal adverse effects were observed in any of the patients. It is important to note that no adverse effects were observed with any of the antibiotics that would preclude further tolerance testing. The type of antibiotic used was found to be significantly associated with tolerance. The proportion of colistimethate administrations that were tolerated was 89.6%, compared to 69.5% for gentamicin ($P < 0.001$) and 69.1% for ampicillin ($P < 0.001$). The probability of a patient showing intolerance was found to be 5.69 times greater for gentamicin ($P < 0.001$) and 6.21 times greater for ampicillin ($P < 0.001$), respectively, compared to colistimethate. No significant difference was observed between the tolerance levels of ampicillin and gentamicin. It is worth noting that some patients who demonstrated colistimethate intolerance were tolerant to ampicillin or gentamicin (data not shown). Conversely, some patients who demonstrated gentamicin intolerance were tolerant to ampicillin (and vice versa).

The univariate analysis was conducted to ascertain which patient variables were associated with intolerance (Table 2). Factors that may have been associated with antibiotic intolerance included smoking habit, a worse post-bronchodilator FEV_1% predicted, and a diagnosis of COPD. The remaining variables did not exhibit any notable correlation with intolerance, as illustrated in Table 2. Multivariate analysis was used to determine the most significant predictors of tolerance. The significant variables used in the analysis were type of antibiotic, post-bronchodilator FEV_1, COPD diagnosis, and smoking habit. In the final model, after adjustment for confounders, the only factor that significantly increased the odds of intolerance was the type of antibiotic (Table 3).

The analysis of interaction and subgroup models to ascertain differences in tolerance according to antibiotic type and different cut-off values of post-bronchodilator FEV_1% predicted revealed no statistically significant differences ($P = 0.72$) (Table 4). The same statistical model was employed to investigate any differences in tolerance according to antibiotic type and the presence or absence of BHR. No statistically significant differences were observed ($P = 0.68$) (Table 5). When sensitivity tests were performed on patients who had been administered all three antibiotics, the results were comparable to those obtained from the entire study population (Supplementary Table A.1).

Symptoms of intolerance

The most common adverse reactions reported by intolerant patients were nausea/bad taste in the mouth (22.8% of patients), followed by cough (21.5%) and dyspnea (17.7%). Of the 79 patients who demonstrated intolerance to at least one administration of any antibiotic, 33 (41.8%) were intolerant according to self-reported symptoms only (Likert test), 25 (31.6%) because of impaired FEV_1 only, 10 (12.7%) as a consequence of both (symptoms and impaired FEV_1), and 11 (13.9%) according to medical criteria.

Discussion

In this study, we evaluated the tolerability of colistimethate and two intravenous antibiotic formulations delivered via inhalation (gentamicin and ampicillin) in patients with BI and/or CBI and/or recurrent respiratory infections. We demonstrated that the only factor influencing tolerability was the type of antibiotic used. We also showed that colistimethate sodium was better tolerated than ampicillin and gentamicin. This study is important because the use of intravenous antibiotic formulations delivered by inhalation is controversial, and some treatment guidelines advise against this type of administration when the same antibiotic is available in an inhalation formulation.[1] However, almost 70% of ampicillin and gentamicin doses were tolerated by patients. Although ampicillin and gentamicin were less well tolerated than colistimethate, in the absence of comparative studies on the efficacy of the different antibiotics, the fact that these formulations are much cheaper than colistimethate or specific antibiotics for inhalation should be taken into account.

This is the first study to compare the tolerability of several antibiotics in the same patients using the same standardized protocol. Other studies have looked at the tolerability of some inhaled antibiotics, but their results cannot be extrapolated to ours. For example, Nikolaizik et al. tested the tolerability of different formulations of tobramycin, but the study was conducted in patients with cystic fibrosis.[15,16] Other authors have used gentamicin in patients with bronchiectasis, but previously excluded patients intolerant to gentamicin.[3] Consequently, the true tolerance to this antibiotic cannot be known. Dennis et al. conducted a study comparing different inhaled therapies in patients with different chronic lung diseases,[17] but not all patients were bronchodilated as recommended by guidelines.

The fact that less than a third of patients failed to tolerate any antibiotic on the basis of lung function alone means that, although lung function is an important criterion, other criteria should also be used, such as clinical criteria (assessment of patient-reported symptoms or monitoring by healthcare professionals).[8] Indeed, in line with the research conducted by Terpstra et al., we observed that when adequate bronchodilation was administered, there was minimal decrease in lung function after inhaled antibiotic therapy.[18] Statistical analyses with interaction models and subgroups according to different FEV_1 cut-off points confirm this fact. Contrary to most studies which find that the most common sign of intolerance to inhaled antibiotics is wheezing and bronchospasm,[3,5] in our

Table 2
Univariate analysis of factors potentially related to intolerance.

Factor	Number of administrations not tolerated	Number of administrations tolerated	OR (95% CI)	*P*-value	Overall *P*-value*
Antibiotic					
Colistimethate	13 (10.4%)	102 (89.6%)	–	–	<0.001
Gentamicin	32 (30.5%)	73 (69.5%)	5.69 (2.27, 14.22)	<0.001	
Ampicillin	34 (30.9%)	76 (69.1%)	6.21 (2.45, 15.70)	<0.001	
Associated factors					
*Age (years)**	68.2 (14.5)	68.2 (13.8)	0.99 (0.97, 1.03)		0.986
Gender					
Male	37 (21.8%)	133 (78.2%)	–	–	
Female	42 (26.3%)	118 (73.7%)	1.32 (0.65, 2.69)		0.437
Smoking habits					
Never-smoker	26 (18.1%)	118 (81.9%)	–	–	0.099
Former smoker	43 (26.9%)	117 (73.1%)	1.90 (0.89, 4.03)	0.097	
Current smoker	10 (38.5%)	16 (61.5%)	3.42 (0.94, 12.43)	0.061	
CBI due to Pseudomonas aeruginosa					
No	48 (21.6%)	174 (78.4%)	–	–	0.282
Yes	31(28.7%)	77 (71.3%)	1.49 (0.72, 3.11)		
*Infectious exacerbations during the year before the tolerance tests**	3.7 (3.0)	3.9 (3.2)	0.98 (0.87, 1.09)		0.670
*Dyspnea (mMRC)**	1.6 (0.9)	1.4 (1.0)	1.36 (0.93, 1.97)		0.111
*Post-bronchodilator FEV_1% predicted**	58.7 (28.0)	68.2 (24.0)	0.98 (0.97, 1.00)		0.014
Presence of bronchiectasis					
No	33 (27.0%)	89 (73.0%)	–	–	0.302
Yes	46 (22.1%)	162 (77.9%)	0.68 (0.32, 1.42)		
FACED score					
Mild	27 (23.1%)	90 (76.9%)	–	–	0.929
Moderate	13 (21.3%)	48 (78.7%)	0.87 (0.30, 2.55)	0.804	
Severe	6 (20.0%)	24 (80.0%)	0.78 (0.20, 3.10)	0.727	
Presence of COPD					
No	39 (19.0%)	166 (81.0%)	–	–	0.016
Yes	40 (32.0%)	85 (68.0%)	2.50 (1.19, 5.26)		
BHR					
No	69 (24.5%)	213 (75.5%)	–	–	0.563
Yes	10 (20.8%)	38 (79.2%)	0.73 (0.25, 2.11)		

BHR: bronchial hyperresponsiveness; CBI: chronic bronchial infection; COPD: chronic obstructive lung disease; FEV_1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council.
* Continuous variables presented as mean (standard deviation).

Table 3
Multivariate analysis of factors potentially related to intolerance.

Factor	Number of administrations not tolerated	Number of administrations tolerated	OR (95% CI)	*P*-value
Antibiotic				
Colistimethate	13 (11.4%)	101 (88.6%)	–	–
Gentamicin	32 (30.5%)	73 (69.5%)	5.83 (2.33, 14.61)	<0.001
Ampicillin	34 (30.9%)	76 (69.1%)	6.56 (2.59, 16.61)	<0.001
Smoking habits				
Never-smoker	26 (18.1%)	118 (81.9%)	–	–
Former smoker	43 (26.9%)	117 (73.1%)	1.25 (0.37, 4.16)	0.713
Current smoker	10 (40.0%)	15 (60.0%)	2.68 (0.47, 15.14)	0.265
*Post-bronchodilator FEV1% predicted**	58.7 (28.0)	68.2 (24.0)	0.98 (0.96, 1.00)	0.110
COPD				
No	39 (19.0%)	166 (81.0%)	–	–
Yes	40 (32.3%)	84 (67.7%)	1.57 (0.40, 6.21)	0.523

COPD: chronic obstructive lung disease; FEV_1: forced expiratory volume in 1 second.
* Continuous variables presented as mean (standard deviation).

study it was nausea or bad taste in the mouth, Moreover, we also found that intravenous formulations were more frequently associated with bad taste in the mouth and nausea than colistimethate.

The precise mechanisms underlying the reduced tolerability of intravenous antibiotic formulations delivered by inhalation in comparison to specific inhalation formulations are not well understood. The pH, osmolarity and the use of preservatives (mainly phenol) in intravenous formulations have been postulated.[19,20] It has been suggested that the solutions should have a pH of 2.6–10 and an osmolarity of 150–1200 mOsm/kg to promote tolerance.[21] All commercial solutions, including colistimethate, have a pH and osmolarity within the recommended pH range. However, the gentamicin and ampicillin used in our study did not.[20] These factors may explain the poorer tolerance of ampicillin and gen-

Table 4
Subgroup analysis according to type of antibiotic used and different cut-off values of post-bronchodilator FEV1% predicted.

Factor	Cut-off values of post-bronchodilator FEV_1% predicted									*P*-value
	0–29%			30–49%			≥50%			
	Number not tolerated	Number tolerated	OR (95% CI)	Number not tolerated	Number tolerated	OR (95% CI)	Number not tolerated	Number tolerated	OR (95% IC)	
Antibiotic										
Colistimethate	4 (30.8%)	9 (69.2%)	–	5 (20.8%)	19 (79.2%)	–	4 (5.2%)	73 (94.8%)	–	0.676
Gentamicin	4 (40.0%)	6 (60.0%)	1.53 (0.22, 10.38)	9 (42.9%)	12 (57.1%)	2.85 (0.77, 10.57)	19 (25.7%)	55 (74.3%)	15.16 (3.17, 72.43)	
Ampicillin	4 (57.1%)	3 (42.9%)	3.08 (0.30, 31.57)	11 (52.4%)	10 (47.6%)	4.18 (1.13, 15.42)	19 (23.2%)	63 (76.8%)	12.05 (2.63, 55.28)	

FEV_1: forced expiratory volume in 1 second.

Table 5
Subgroup analysis according to the type of antibiotic used and the presence or absence of bronchial hyperresponsiveness.

Factor	Bronchial hyperresponsiveness			No bronchial hyperresponsiveness			*P*-value
	Number not tolerated	Number tolerated	OR (95% CI)	Number not tolerated	Number tolerated	OR (95% CI)	
Antibiotic							
Colistimethate	2 (12.5%)	14 (87.5%)	–	11 (11.1%)	88 (88.9%)	–	0.719
Gentamicin	4 (28.6%)	10 (71.4%)	7.11 (0.39, 128.61)	28 (30.8%)	63 (69.2%)	5.56 (2.11, 14.63)	
Ampicillin	4 (22.2%)	14 (77.8%)	4.03 (0.28, 57.32)	30 (32.6%)	62 (67.4%)	6.60 (2.44, 17.84)	

tamicin compared to colistimethate. Typically, 0.9% saline is used for dilution, although water for injection can also be employed. For instance, Murray et al. used a gentamicin injectable solution reconstituted for nebulization with 0.9% saline,[3] while Vélez-Díaz-Pallarés et al. propose a diluted form of antibiotics in normal saline.[20]

Despite the prevailing consensus and guidelines stipulating that a CBI with a PPM is a criterion for the administration of inhaled antibiotics, it is noteworthy that in one third of the patient population, no PPM was identified. Moreover, in more than 20% of bronchiectasis cases, no PPM was detected in lower respiratory tract samples, even in patients exhibiting purulent sputum and recurrent infections.[22] Rogers et al. used pyrosequencing analysis to ascertain that, despite the efficacy of culture-based diagnostic microbiology in the identification of specific respiratory pathogens, other bacterial species may be overlooked.[23] Consequently, the antibiotic response was not always predictable from the results of the sputum culture.

In this study, we did not introduce other specific inhalatory antibiotics, such as tobramycin solution for inhalation, because most patients receive continuous antibiotic treatment due to deterioration in the off cycles (and tobramycin is administered in cycles of 28 treatment days and 28 rest days). It should be noted that the results of this study cannot be extrapolated to other antibiotics, including either specific inhaled antibiotics or intravenous formulations adapted for nebulization.

The present study has several limitations. Firstly, the Likert questionnaire employed to assess tolerability has not been formally validated. The decision to use this particular instrument was influenced by two key factors, i.e., the absence of a validated questionnaire for this purpose and its previous use in related studies.[24] Secondly, the study employed a single test to evaluate antibiotic tolerance. In clinical practice, a percentage of patients (usually in the range of 10%–15%, unpublished results) even if they tolerate the first dose of the drug well, develop intolerance with repeated inhalations (usually in the first week after starting treatment). Therefore, our study overestimates the real tolerance to inhaled antibiotics in chronic treatment. In addition, mainly due to the COVID-19 pandemic, 45% of the patients did not undergo the three tolerance tests. However, the application of sensitivity analyses, restricted to the 75 patients who received the three tests, yielded similar results, thereby enhancing the robustness of the study.

Conclusion

In conclusion, our study shows that in patients with BI and/or CBI and/or recurrent exacerbations, inhaled colistimethate sodium is better tolerated than intravenous formulations of ampicillin and gentamicin delivered by nebulization. The only factor influencing tolerability is the type of antibiotic used.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used DeepL Translate in order to improve English. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Authors' contributions

L.M.C. is the guarantor of the article, data and analysis. L.M.C., R.N.R., D.D.B., E.B.H., M.V.-D.-P. and R.M.G. were involved in the concept and design of the study, as well as the interpretation of the data. J.M.M., G.R-C. and A.M.G. conducted the statistical study. All authors participated in the acquisition of the data, critical revision of major intellectual content, drafting of the manuscript and approval of the version to be published.

Conflicts of interest

The authors declare that they have no conflict of interest in relation to the subject matter.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.opresp.2025.100460.

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