

# Inhaled Colistimethate Sodium in the Management of Patients with Bronchiectasis Infected by *Pseudomonas aeruginosa*: A Narrative Review of Current Evidence

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**Abstract:** International guidelines on the treatment of bronchiectasis indicate that the use of inhaled antibiotics is effective, especially in symptomatic chronic bronchial infection (CBI) due to *Pseudomonas aeruginosa* (PA). To date, however, no such treatment has been approved by regulatory agencies. Of the inhaled antibiotics on the market, colistimethate sodium (colistin) is one of the most used in many countries, either in its nebulized presentation or as dry powder. Among the characteristics of this antibiotic, it is worth noting that its main target is the lipopolysaccharide in the outer membrane of the cell wall of gram-negative bacteria and that it has a low rate of resistance to PA (<1%). Most observational studies have shown that the use of colistin in patients with bronchiectasis and CBI due to PA results in a decrease in both the number and severity of exacerbations, an improvement in quality of life, a decrease in sputum volume and purulence, and a high rate of PA eradication, although there are no clear differences with respect to other inhaled antibiotics. However, the lack of randomized clinical trials (RCT) with positive results for its main variable (exacerbations) in an intention-to-treat analysis has prevented its approval by regulatory agencies as a formal indication for use in bronchiectasis. The PROMIS program, made up of two RCT with identical methodology, is currently underway. The first of these RCT (already concluded) has demonstrated a clearly positive effect on the group randomized to colistin in its main variable (number of annual exacerbations), while the results of the second are still pending. This review presents exhaustive information on the pharmacological and microbiological characteristics of colistin, the results of the studies carried out to date, and the future challenges associated with this treatment.

**Keywords:** colistin, nebulized antibiotics, pharmacology, chronic bronchial infection, COPD

## Introduction

Most studies on the efficacy of inhaled antibiotics have generally been performed in cystic fibrosis (CF) patients, and their use in this disease is recommended by all scientific societies.<sup>1</sup> Since inhaled antibiotics showed a remarkable improvement in the evolution of CF patients, their use was gradually extended to regular clinical practice in patients with non-CF bronchiectasis (hereafter called bronchiectasis) who had frequent isolations of *Pseudomonas aeruginosa* (PA), despite the lack of any formal indication in these drugs' information leaflets. This widespread practice has created a body of evidence over time (mainly in the form of observational studies), which eventually became sufficient for the use of inhaled antibiotics in general, and colistin in particular, to be included among the recommendations of the various national and international treatment guidelines for bronchiectasis.<sup>2-4</sup> These developments have inspired research into new molecules and new ways of dispensing inhaled antibiotics, as well as the instigation of various clinical trials whose results will emerge in the coming years.

In recent years, it has been shown that the presence of certain potentially pathogenic microorganisms (PPM), especially PA, is associated with a poorer clinical course, regardless of whether a patient's underlying lung disease is CF, bronchiectasis, or even chronic obstructive pulmonary disease (COPD). Accordingly, concepts such as primary infection and chronic bronchial infection (CBI) have emerged, allowing a patient to be categorized as being at risk of progressive clinical deterioration and, therefore, a potential candidate for early and/or prolonged antibiotic treatment. There has been an increasing tendency to use inhaled antibiotics to treat these patients, due to their greater bioavailability at the site of infection and lower frequency of systemic side effects.

Although tobramycin has been the most widely studied inhaled antibiotic, its association with local and systemic side effects and the frequency of antibiotic resistance, as well as the clinical worsening of many patients in treatment rest periods, has motivated the search for alternative antibiotics.<sup>1</sup> These include colistin or colomycin, an old acquaintance in the field of respiratory infections that fell into disuse due to its side effects when administered systemically. Since the end of the last century, however, there has been far-reaching research into the effectiveness and safety of nebulized colistin in patients with CF and chronic or intermittent bronchial infection by PA, giving rise to a resurgence that has now made it one of the pillars of treatment for these patients.<sup>5,6</sup> This development led to the use of colistin in bronchiectasis patients, in both clinical practice and research.

In this article, we review various issues related to the use of colistin in bronchiectasis, such as the deleterious consequences of CBI, the recommendations of the scientific societies regarding the use of inhaled antibiotics in bronchiectasis, and the pharmacological characteristics of colistin, as well as the published scientific evidence regarding its effectiveness and safety.

## Why Chronic Bronchial Infection by *Pseudomonas aeruginosa* and Exacerbations are Important in Bronchiectasis

CBI is one of the key elements of the “vicious vortex” hypothesis in the pathogenesis of bronchiectasis, in which bacteria induce a sustained inflammatory response that leads to further airway structural damage.<sup>7</sup> CBI is defined as three or more consecutive positive cultures for the same PPM in a period of at least 6–12 months, with a time span between samples of at least one month.<sup>8</sup> PA is one of the most common PPM isolated in the airway samples of bronchiectasis patients, causing chronic infection in up to 25% of them.<sup>9,10</sup> PA rapidly adapts to the chronically infected lung by developing antibiotic resistance and forming biofilms to protect itself from the immune system and the effect of antibiotics.<sup>11,12</sup> The eradication of PA is thus a treatment priority in bronchiectasis patients, as managing CBI by this pathogen is a major clinical challenge.<sup>2,3</sup>

The negative effects of PA infection on bronchiectasis patients have been widely studied. In fact, PA-CBI is a marker for disease severity in internationally validated scores such as the Bronchiectasis Severity Index (BSI), the FACED and E-FACED.<sup>13–15</sup> In terms of lung function, Martinez-Garcia et al observed that chronic PA infection, frequent exacerbations, and systemic inflammation were associated with a faster worsening of the disease.<sup>16</sup> Similarly, another study including 849 patients from the Spanish Bronchiectasis Registry (RIBRON) showed that the annual decline of the forced expiratory volume during the first second (FEV<sub>1</sub>) was faster in individuals with PA-CBI (−1.37% (52.1 mL) vs −0.37% (−24.6 mL);  $p < 0.001$ ), older age, increased number of previous severe exacerbations, and higher FEV<sub>1</sub> at baseline.<sup>17</sup>

PA has also been shown to play a significant role in bronchiectasis mortality. Chalmers et al observed a mortality rate of 21.2% in bronchiectasis patients with PA-CBI in the BSI cohort,<sup>13</sup> while Martinez-Garcia et al found that it was 48.1% in the FACED cohort.<sup>14</sup> A Belgian study prospectively assessed mortality in 245 bronchiectasis individuals and identified a hazard ratio (HR) of 1.60 (95% confidence interval [CI] 1.27–2.00;  $p$ -value  $< 0.0001$ ) for mortality in patients chronically infected with PA.<sup>18</sup> Another long-term study by Loebinger et al showed that age, St. George's Respiratory Questionnaire (SGRQ) score, PA infection, and lung volumes and diffusion capacity were all independently associated with mortality.<sup>19</sup> Finally, a comprehensive analysis by Finch et al, which included these and several other studies to evaluate the impact of PA on the prognosis of adult patients with bronchiectasis, observed a pooled odds ratio [OR] for mortality of 2.95 (95% CI 1.98–4.40;  $p$ -value 0.0001) for subjects with PA-CBI.<sup>10</sup>

Furthermore, PA has also shown a significant correlation with frequent exacerbations. Rogers et al stratified 107 bronchiectasis patients into three groups, according to the predominant microbiota taxon: PA, *Haemophilus influenzae*, and other taxa. PA predominance was the best predictor of frequent future exacerbations in this cohort.<sup>20</sup> The aforementioned comprehensive analysis also showed that PA-CBI was significantly associated with a higher number of hospital admissions (OR 6.57; 95% CI 3.19–13.51; p-value 0.0001) and exacerbations (mean difference 0.97/year; 95% CI 0.64–1.30; p-value 0.0001), as well as poorer quality of life, as defined by the SGRQ score (mean difference 18.2 points; 95% CI 14.7–21.8; p-value 0.0001).<sup>10</sup> It is therefore safe to consider PA infection as not only a marker of severe bronchiectasis but also a significant driver of disease progression.

Exacerbations are another key element in the pathogenesis of bronchiectasis. Both the number and severity of exacerbations have been associated with a poorer clinical prognosis in terms of quality of life, lung function decline, increased costs, and mortality.<sup>13,15,21,22</sup> In a recent multicenter study including 651 patients, the definition of frequent exacerbator that presented the greatest predictive power for mortality was based on at least two exacerbations/year or one hospitalization/year (area under the curve [AUC]-ROC: 0.75; 95% CI: 0.69–0.81).<sup>21</sup> Frequent exacerbations are the strongest predictors of further frequent exacerbations in the future, while 5-year mortality is higher with an increasing number of exacerbations.<sup>23</sup> The prevention and prompt management of acute exacerbations are therefore crucial for avoiding disease progression and reducing patient mortality.

## Indications of Inhaled Antibiotics in International Guidelines in Bronchiectasis

The indications for the administration of inhaled antibiotics in patients with bronchiectasis have not been well defined and thus vary between the different management guidelines; their most relevant aspects are described in [Tables 1 and 2](#).

Due to the good microbiological results of inhaled antibiotic treatment in patients with BE and PA primary infection, most treatment guidelines include the inhaled route as a means to eradicate this microorganism. Among the different recommendations for treatment of PA primary infection, inhaled antibiotics are usually included, as a first, second, or third line of attack. The eradication of other PPMs is not generally suggested, except in the Spanish guidelines, even though their eradication protocols recommend only the use of oral or intravenous – not inhaled – antibiotics ([Table 1](#)).

As regards CBI by PA, all but one of the guidelines recommend treatment with inhaled antibiotics, although with slight variations in the type of antibiotics and the protocols to be used. In CBI by other PPMs, there is more variation in the recommendations, to such an extent that several current guidelines do not recommend any treatment for them. It should be pointed out that the Spanish guidelines stand alone in always recommending inhaled antibiotics as the first therapeutic option in patients with CBI ([Table 2](#)).

## Inhaled Sodium Colistimethate Pharmacokinetics and Pharmacodynamics

Polymyxins are a group of polypeptide antibiotics that include several different compounds, of which only polymyxin B and E (colistin) have clinical applications. Colistin is a multicomponent antibiotic made up of a complex mixture of about 30 different decapeptides. Its two main components are colistin A (polymyxin E1) and colistin B (polymyxin E2), which typically account for more than 85% of colistin, but the proportion of these constituents can vary substantially between different pharmaceutical formulations.<sup>24</sup>

There are two pharmaceutical forms of colistin: colistin sulfate, for topical and oral use, and colistin methanesulfonate (available as a sodium salt, known as sodium colistimethate, less toxic than colistin sulfate), for injection and inhalation. Sodium colistimethate (SCM) is an inactive prodrug. It is hydrophilic and polyanionic at a pH of 7.4, and it contains the colistin moiety, with a sulfomethyl group added to the primary amines of colistin. Its hydrolysis produces the active drug colistin, along with other derivatives.<sup>25</sup> Colistin is polycationic at a pH of 7.4 and hydrophilic but, due to the presence of both lipophilic and hydrophilic groups, it has amphipathic property.<sup>24</sup> It is advisable not to use the terms colistin and SCM interchangeably because their chemistry, pharmacokinetics, pharmacodynamics, and toxicity are different.<sup>26</sup>

**Table I** Indication for Inhaled Antibiotic Treatment in Patients with Bronchiectasis and Primary Bronchial Infection (Presented in Chronological Order of Their Publication Date)

First Author Medical Society Year of Publication	Recommendations	Protocols	Inhaled Antibiotics Used	Comments
<b>Chang, AB Thoracic Society of Australia and New Zealand Guidelines 2015<sup>92</sup></b>	When <i>P. aeruginosa</i> is first detected, consider discussion with a specialist in this field regarding the suitability of eradication treatment. No recommendations for other PPMs.	No protocols.	No antibiotics listed.	No comments.
<b>Polverino, E European Respiratory Society Guidelines 2017<sup>3</sup></b>	Patients with a new isolation of <i>P. aeruginosa</i> should be offered eradication antibiotic treatment. Do not offer eradication antibiotic treatment to patients following new isolation of pathogens other than <i>P. aeruginosa</i> .	Three possible and alternative <i>P. aeruginosa</i> eradication treatment pathways based on usual clinical practice.	Colistin or tobramycin solution for inhalation or gentamicin*.	There is no clear evidence to support one regimen over another. After each step it is recommended to repeat sputum sampling and to progress to the next step if the culture remains positive.
<b>Al-Jahdali, H Saudi Thoracic Society Guidelines 2017<sup>93</sup></b>	No recommendation.	No protocols.	No antibiotics listed.	There is a need for more studies on the effectiveness of <i>P. aeruginosa</i> eradication.
<b>Martínez-García, MA Spanish Respiratory Society Guidelines 2018<sup>2</sup></b>	Eradication of <i>P. aeruginosa</i> should be attempted. Eradication of MRSA should be attempted. For other PPMs, the decision to apply an eradication treatment in initial infection should be made on an individual basis, according to the patient's symptoms and the PPMs in question.	Several protocols for <i>P. aeruginosa</i> eradication. Several protocols for MRSA eradication.	Aztreonam lysine solution for inhalation, colistin or tobramycin solution for inhalation. One includes inhaled vancomycin*. Gentamicin* or any of the inhaled antibiotics used in chronic <i>P. aeruginosa</i> infection.	No eradication protocol has shown superiority over another.
<b>Hill, AT British Thoracic Society Guidelines 2019<sup>4</sup></b>	Offer eradication antibiotic treatment to patients with clinical deterioration and a new growth of <i>P. aeruginosa</i> . No recommendation with inhaled antibiotics for PPMs other than <i>P. aeruginosa</i> .	Several protocols for <i>P. aeruginosa</i> eradication, according to the clinical situation.	Colistin, gentamicin* or tobramycin* or tobramycin solution for inhalation.	Discuss with patients the potential risks and benefits of starting eradication treatment versus clinical observation in the context of stable bronchiectasis.
<b>Pereira, MC Brazilian Consensus 2019<sup>94</sup></b>	Immediately following the first identification of <i>P. aeruginosa</i> , the patient should be treated with a systemic antipseudomonal antibiotic combined with an inhaled antibiotic. With regard to other PPMs, there is insufficient evidence to justify the adoption of eradication protocols in this context.	Suggest a 14- to 21-day regimen of systemic antibiotic therapy in conjunction with a longer than 3-month course of inhaled antibiotic. No protocols listed.	Colistin, gentamicin* or tobramycin (solution for inhalation). No antibiotics listed.	If inhaled antibiotics are unavailable, treatment should consist only of systemic antibiotics. In selected cases, characterized by progressive functional decline and/or severe exacerbation related to the first identification of a PPMs, eradication should be undertaken.

**Note:** \*Intravenous formulation administered via inhalation.

**Abbreviations:** *P. aeruginosa*, *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PPM, potentially pathogenic microorganisms.

**Table 2** Indication for Inhaled Antibiotic Treatment in Patients with Bronchiectasis and Chronic Bronchial Infection (Presented in Chronological Order of Their Publication Date)

First Author Medical Society Year of Publication	Recommendations	Protocols	Inhaled Antibiotics Used	Comments
<b>Chang, AB Thoracic Society of Australia and New Zealand Guidelines 2015<sup>92</sup></b>	Long-term nebulised antibiotics against <i>P. aeruginosa</i> infection should not be prescribed routinely. No recommendations in patients with chronic bronchial infection due to other PPMs.	Consider a therapeutic trial in patients with frequent exacerbations and/or <i>P. aeruginosa</i> infection.	No antibiotics listed.	No comments.
<b>Polverino, E European Respiratory Society Guidelines 2017<sup>3</sup></b>	Authors suggest long-term treatment with an inhaled antibiotic for patients with chronic <i>P. aeruginosa</i> infection and three or more exacerbations per year. Authors suggest long-term treatment with an inhaled antibiotic for patients not infected with <i>P. aeruginosa</i> in whom neither oral antibiotic prophylaxis nor macrolide treatment is tolerated or effective.	For individuals with <i>P. aeruginosa</i> , the currently available evidence supports continuous use of nebulized colistin or gentamicin.	For any PPMs (including <i>P. aeruginosa</i> ): colistin or gentamicin*. Nebulized aztreonam is not recommended.	Long-term antibiotic therapy should be considered only after optimization of general aspects of bronchiectasis management.
<b>Al-Jahdali, H Saudi Thoracic Society Guidelines 2017<sup>93</sup></b>	Benefits of long-term inhaled antibiotics are not clear and authors do not recommend their use.	No protocols listed.	Tobramycin (solution for inhalation), gentamicin* or colistin.	Authors do not recommend routine use of inhaled antibiotics, except in very select cases with chronic <i>P. aeruginosa</i> infection, frequent exacerbation, and significant morbidity.

(Continued)

Table 2 (Continued).

First Author Medical Society Year of Publication	Recommendations	Protocols	Inhaled Antibiotics Used	Comments
<b>Martínez-García, MA</b> <b>Spanish</b> <b>Respiratory</b> <b>Society</b> <b>Guidelines 2018<sup>2</sup></b>	Prolonged antibiotic treatment is recommended in the following situations: <ul style="list-style-type: none"> <li>• In all patients who present chronic bronchial <i>P. aeruginosa</i> infection.</li> <li>• In patients with chronic bronchial infection due to other PPMs, who also present at least 2 exacerbations or 1 hospitalization due to exacerbation during the previous year; marked decline in lung function, or deterioration in quality of life evidenced by an increase in sputum volume or purulence, dyspnea, or cough.</li> </ul>	Several protocols for <i>P. aeruginosa</i> and other PPMs in chronic bronchial infection.	<ul style="list-style-type: none"> <li>• Chronic bronchial <i>P. aeruginosa</i>: nebulized aztreonam or **ciprofloxacin (dry powder or solution for inhalation) or colistin (dry powder or solution for inhalation) or gentamicin* or tobramycin (dry powder or solution for inhalation).</li> <li>• Chronic MRSA infection should be treated with vancomycin*.</li> <li>• Chronic <i>Stenotrophomonas maltophilia</i> infection should be treated with colistin.</li> <li>• Chronic infection with other PPMs should be treated with gentamicin* or any of the inhaled antibiotics used in chronic <i>P. aeruginosa</i> infection.</li> </ul>	Inhaled rather than systemic antibiotics are strongly recommended. Treatment protocols for chronic infection are varied and none has demonstrated superiority over another.
<b>Hill, AT</b> <b>British</b> <b>Thoracic Society</b> <b>Guidelines 2019<sup>4</sup></b>	Consider long-term antibiotics in patients who experience 3 or more exacerbations per year.	<i>P. aeruginosa</i> -infected patients: Colistin. Consider inhaled gentamicin as a second line. Non- <i>P. aeruginosa</i> -infected patients: Consider inhaled gentamicin* as a second line alternative to macrolides.	Gentamycin*, tobramycin (solution for inhalation) or colistin.	Thresholds for long term treatment may be reduced if the patient is symptomatic between exacerbations and/or the exacerbations respond poorly to treatment and/or the patient is at high risk of severe exacerbation.
<b>Pereira, MC</b> <b>Brazilian</b> <b>Consensus</b> <b>2019<sup>94</sup></b>	Patients with chronic <i>P. aeruginosa</i> infection and exacerbations should be treated with long-term inhaled antibiotics. In patients with chronic infection with PPMs other than <i>P. aeruginosa</i> , the lack of evidence does not allow any recommendation of the use of inhaled antibiotics.	No protocols listed.	Colistin, gentamicin*, tobramycin (dry powder or solution for inhalation).	The choice will depend on the availability of and access to medication.

**Note:** \*Intravenous formulation administered via inhalation; \*\*Not yet on the market.

**Abbreviations:** *P. aeruginosa*, *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PPM, potentially pathogenic microorganisms.

There are relatively few PK and PD studies on colistin or SCM in humans, and many of these have been carried out in special populations, such as subjects with cystic fibrosis or critically ill patients. After intravenous administration to healthy volunteers, SCM has a terminal half-life of 2 hours, while the terminal half-life of the active compound colistin is 3 hours.<sup>27</sup> After administration, SCM is partially converted to colistin by hydrolysis. The main mechanism for clearing unconverted SCM is renal excretion, but, in contrast, the renal clearance of colistin is low, due to extensive tubular reabsorption. The mechanisms for the elimination of colistin remain largely unknown, although it is believed to be eliminated by hydrolysis.<sup>24</sup> After intravenous administration, the physicochemical characteristics of SCM and colistin predispose to low penetration into lung tissue, due to their large molecular weights and electric charge. The distribution within the lungs after parenteral administration is therefore believed to be low. In fact, studies have found that, after several dose-regimen administrations of intravenous SCM, the bronchoalveolar lavage and sputum concentrations of the active colistin drug were low,<sup>28,29</sup> below the susceptible breakpoint of  $\leq 2$  mg/L established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) for *P. aeruginosa*.<sup>30</sup> However, other authors have found variable concentrations of colistin in the epithelial lining fluid (ELF), ranging from 1.48 to 28.9 mg/L, after intravenous administration of 2 million international units (MIU) of SCM.<sup>31</sup>

PK parameters may vary substantially in patients compared to healthy volunteers. After intravenous administration, the half-life of SCM will change depending on the volume of distribution, which is a dynamic variable, particularly in critically ill patients, where it fluctuates according to variations in albumin, the infusion of liquids, etc. Moreover, impaired renal function decreases the clearance of SCM and increases the fraction converted to colistin.<sup>32</sup> Consequently, it is difficult to predict the PK of colistin (and, accordingly, the drug's efficacy and toxicity) when intravenous administration is used in these populations. Dose-limiting nephrotoxicity is a significant concern with the parenteral administration of SCM. This, coupled with low lung penetration, makes intravenous SCM a suboptimal drug for treating respiratory tract infections.

As regards the PD of colistin, it can, depending on its concentration, kill susceptible strains of pathogens like PA, with a very modest post-antibiotic effect that is seen only at high, non-clinically relevant concentrations. Studies investigating the relationship between the PK and PD of colistin have evaluated several integrated PK/PD parameters, such as the peak plasma concentrations ( $C_{max}$ ) to minimum inhibitory concentration (MIC) ratio ( $C_{max}/MIC$ ), the time above the MIC ( $T_{>MIC}$ ), and the area under the concentration curve (AUC) to MIC ratio (AUC/MIC).<sup>33</sup> Although early animal studies suggested that once-daily dosing of colistin was most effective against PA and, therefore, that  $C_{max}/MIC$  might be the most useful PK/PD index for predicting activity, further studies have shown that the most predictive PK/PD index of antibacterial activity is the free (unbound) AUC to MIC ratio ( $fAUC/MIC$ ), suggesting that time-averaged exposure to colistin is significant for its antibacterial activity and that the drug has both concentration- and time-dependent effects.<sup>33</sup>

Furthermore, relatively few PK and PD studies of colistin using the inhalation route have been undertaken to date, in either animal models or humans. These studies agree, however, that high levels of colistin exposure are achieved in epithelial lining fluid (ELF) and sputum after inhalation, and that these levels are much higher than after intravenous administration.<sup>29,31,34–38</sup> Systemic exposure after SCM inhalation is low. Concentrations of SCM and colistin can be on the order of 100 to 1000 times higher in the ELF than in plasma after administration of aerosolized SCM.<sup>31</sup> Yapa et al found that the systemic availability of SCM was low after the administration by nebulizer of 2 and 4 MIU of SCM (7.93% and 5.37%, respectively).<sup>29</sup> Boisson et al also found that, after aerosol delivery, only about 9% of the SCM dose reached the systemic circulation.<sup>31</sup> In contrast, a much higher systemic bioavailability (46 to 64%) have been observed in rat models after intratracheal administration.<sup>35,36</sup> The reason for this difference is unclear, but it has been speculated that the diffusion of colistin across the bronchial epithelium is not only mediated by passive diffusion and that specific drug transporters might be implicated in the absorption of colistin – and the expression of these transporters might be different between species.<sup>34</sup>

The substantial pulmonary exposure and minimal systemic exposure observed after inhalation of SCM in humans imply that this route should be effective in maximizing the antibacterial effect in the respiratory system, while also minimizing toxicity. There are some limitations, however, in the interpretation of the PK/PD data for colistin when the inhalation route is used. Studies using sputum samples may not adequately reflect the drug concentrations in the lower respiratory tract. Consequently, reliable pharmacokinetic data are often based on the measurement of a drug's serum

concentrations, but these may also inadequately reflect pulmonary drug exposure.<sup>31,38</sup> PK/PD targets have been defined to maximize the effect of colistin when used intravenously.<sup>30</sup> As mentioned above, the relevant PK/PD parameter for colistin is plasma  $fAUC/MIC$  but since plasma concentrations of colistin do not reflect lung concentrations and therefore cannot be used to compare antimicrobial activity in the lungs after SCM administration in aerosol form, a specific ELF  $fAUC/MIC$  should be defined. To overcome these problems, PK-PD modeling approaches have been used, predicting a clear superiority of SCM using the inhalation route over intravenous administrations with respect to antimicrobial activity.<sup>31</sup>

Ratjen et al found that maximum colistin concentrations in the sputum of CF patients peaked 1h after inhalation of SCM, reaching levels at least 10 times higher than the MIC for PA. Significantly, mean concentrations were still above the MIC breakpoint 12h after administration.<sup>38</sup> These results support the use of a twice-daily dosing regimen. In contrast, Athanassa et al found, in mechanically ventilated patients treated with inhaled SCM, that the median ELF colistin concentrations were above the MIC of the isolated pathogens at 1 and 4h, but decreased at 8h. The differences in the dose of SCM used in both studies (80 mg every 8h in the Athanassa study and 2 MIU – corresponding to 160 mg of SCM – every 12h in the Ratjen study) may explain these differences.

There are some other areas of uncertainty regarding the PK and PD studies of inhaled colistin. The PK parameters vary widely between studies, and even between individuals within the same study.<sup>31,37</sup> The heterogeneity of the populations studied, with a variable degree of disease severity, could partially explain these discrepancies. Furthermore, some studies used sputum samples, which are not homogeneous, and most likely reflect drug deposits in the large rather than the smaller airways.<sup>29,38</sup> Studies obtaining samples from the lower airways have used sampling methods (mini-bronchoalveolar lavage) that could sample different lung sections in different patients.<sup>31,37</sup> The PK and PD variables could plausibly be different for the same drug, according to whether dry powder or solution formulations are used for administration by inhalation. Tewes et al found a lower exposure of the pulmonary epithelial lining fluid to colistin after intratracheal administration of SCM powder to rats, compared to SCM solution.<sup>36</sup> However, they attributed this difference to faster systemic absorption of the drug after the inhalation of powder and, as mentioned above, the PK of SCM absorption might be different in humans. Even using the same formulation, the PK could be different, depending on the delivery system (ie, the design of the nebulizer), although Ratjen et al found no significant differences in sputum colistin concentrations with two different nebulizers.<sup>38</sup> It should be mentioned that new inhalable formulations are being developed that combine colistin with other antibiotics, like ciprofloxacin and meropenem, and specific PK/PD studies will be needed with these new formulations, as well as with future nanomedicine-based delivery systems.<sup>39–41</sup>

## Microbiological Properties

Colistin is active against aerobic Gram-negative pathogens such as PA, *Haemophilus influenzae*, *Acinetobacter spp*, *Escherichia coli*, and other Enterobacteriaceae such as *Klebsiella spp*, *Salmonella spp*, and *Shigella spp*. Its activity against *Stenotrophomonas maltophilia*, *Aeromonas spp.*, and *Vibrio spp* is variable, and it is not active against some aerobic Gram-negative bacilli, such as *Pseudomonas mallei*, *Burkholderia cepacia*, *Proteus spp*, *Providencia spp*, *Serratia spp*, *Edwardsiella spp*, and *Brucella spp*. It does not exhibit activity against any Gram-positive or Gram-negative cocci (such as *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Moraxella catarrhalis*), fungi, parasites, or against most anaerobes.<sup>42</sup>

The main target of colistin is the lipopolysaccharide (LPS) in the outer membrane of the cell wall of Gram-negative bacteria. The cationic colistin molecule fuses with the bacterial membrane through electrostatic interactions with anionic groups on the lipid A component of the LPS. Colistin then displaces  $Mg^{2+}$  and  $Ca^{2+}$  from the outer cell membrane of the bacteria, destabilizing the membrane structure and leading to the insertion of the colistin molecule into the membrane. This event results in an increase in the membrane permeability, which is followed by leakage of cell contents and bacterial death. Colistin is believed to act through additional mechanisms, such as the production of reactive oxygen species, which causes oxidative damage leading to cellular death, and the inhibition of bacterial respiratory enzymes. In addition to this direct antibacterial effect, colistin could also inhibit the endotoxin activity of the bacterial LPS, suppressing the capacity to induce shock through the release of inflammatory cytokines.<sup>43</sup>



Colistin is one of the few antibiotics that may still be useful for the treatment of infections caused by multidrug-resistant microorganisms such as *A. baumannii* and PA, which have a high tendency to develop multidrug-resistant and other extremely resistant strains, as colistin's resistance mechanisms are quite rare and chromosomally encoded, making transfer difficult. Therefore, the rate of resistance against colistin in Gram-negative pathogens appears to be lower than against that of other classes of antibiotics.<sup>44,45</sup> The primary mechanism underlying colistin resistance seems to reside in modifications to the LPS through the addition of cationic groups that reduce its negative charge, thus reducing electrostatic interactions with the positively-charged colistin. Other proposed resistance mechanisms include mutations leading to loss of LPS (with subsequent loss of the colistin target), overproduction of capsular polysaccharide that hides the colistin binding sites, and enzymatic inactivation of colistin.<sup>43,46</sup>

Colistin resistance can be acquired through colistin-heteroresistant bacteria. Heteroresistance is a form of antibiotic resistance in which a bacterial strain is composed of one minor resistant subpopulation and one largely susceptible subpopulation.<sup>47</sup> Misclassification of heteroresistant isolates as susceptible can lead to unexplained treatment failures. Although the MIC of most bacteria from these strains is  $\leq 2$  mg/l, subpopulations can survive in the presence of concentrations greater than 2 mg/l of colistin, leading to amplification of the resistant subpopulations.<sup>46</sup> This phenomenon, which has been particularly described in the case of *Acinetobacter baumannii*, has been attributed to bacterial exposure to suboptimal doses of colistin. It could therefore be a concern when using inhaled antibiotics, which may reach low (subinhibitory) concentrations in those areas of the lung with more severe structural damage.

In addition to mutation-based resistance mechanisms, another significant area of concern is the transfer between different bacterial species of the plasmid-mediated *mcr-1* gene, which encodes colistin resistance in Gram-negative bacteria.<sup>43</sup> The mechanism by which *mcr-1* induces colistin resistance is similar to that of intrinsically resistant bacteria: ie, it decreases the electrostatic interactions between colistin and LPS.<sup>43</sup> The dissemination of *mcr-1*, first described in 2015 in an *E. coli* strain in China,<sup>48</sup> has now been reported worldwide. It has been found that *mcr-1* alone could, without any additional resistance mechanisms, provide significant resistance to colistin in several Enterobacteriaceae.

## Efficacy and Safety of Colistin in Patients with Bronchiectasis

### Observational Studies

The first descriptions of the use of colomycin in patients with non-cystic fibrosis bronchiectasis date back more than 50 years. These came from small retrospective series of patients with heterogeneous clinical features, in which other inhaled antibiotics were also used and the results were inconclusive, or even contradictory.<sup>49,50</sup> The beginning of this century saw further publications such as Montero et al,<sup>51</sup> which included patients who received both intravenous and inhaled treatment for very different indications, including bronchial infection by PPM in patients with chronic bronchial disease. However, its retrospective design and the heterogeneity of the patients included, with several types of infection and different treatment approaches, do not allow us to draw relevant conclusions about the possible usefulness of colistin in patients with bronchiectasis.

Table 3 summarizes the most relevant observational studies in which the effectiveness and safety of inhaled colistin in patients with bronchiectasis have been specifically assessed. One of the pioneering studies in this field was that of the Australians Steinfert et al,<sup>52</sup> which consisted of a cohort of 18 patients with either bronchiectasis or COPD, along with chronic bronchial sepsis. Their results showed that the administration of nebulized colistin reduced respiratory function loss and improved quality of life in patients with chronic lung disease colonized by susceptible multidrug-resistant PPM, with no appreciable side effects. Despite acknowledging that it was a small study with various limitations that rule out any generalizable conclusions, the authors proposed that colistin could be a useful treatment in patients with poor control of symptoms or frequent hospital admissions. They also suggested an evaluation of its effect on the rate of infectious exacerbations and sputum microbiology, including its possible role in the eradication of PA in patients with persistent colonization despite prolonged antimicrobial therapy.

Some of these questions were addressed shortly afterwards by Dhar et al,<sup>53</sup> who conducted a retrospective study in 19 patients in the United Kingdom affected by bronchiectasis and chronic bronchial colonization by PA. Nebulized colomycin reduced exacerbation frequency, number of hospitalizations, sputum PA positivity, and sputum volume, and

**Table 3** Studies on the Efficacy/Effectiveness and Safety of Colistin in Bronchiectasis Patients, in Chronological Order According to the Year of Publication

First Author Country Publication Year	Type of Study	Objectives of the Study	Inclusion Criteria	Number and Characteristics of Patients Included	Dose and Duration of the Inhaled Treatment	Efficacy / Effectiveness Results	Antibiotic Resistance and Safety Results
Steinfort, DP Australia 2007 <sup>52</sup>	Prospective, non-controlled.	To examine the utility of long-term nebulized colistin in patients with COPD and non-CF bronchiectasis.	Patients with bronchiectasis or severe COPD (FEV <sub>1</sub> <40%), as well as repeated isolates of multi-drug resistant Gram-negative bacteria in sputum cultures with the following clinical features: <ul style="list-style-type: none"> <li>• High rates of exacerbations or admissions to hospital.</li> <li>• Difficulty with symptom control.</li> <li>• High volume of sputum production in between exacerbations.</li> </ul>	18 patients: <ul style="list-style-type: none"> <li>• 14 idiopathic bronchiectasis.</li> <li>• 4 severe COPD/chronic infective bronchitis.</li> </ul> 66% women Age: 69 ± 10.2 years.	Nebulized colistin 30 mg daily Duration: 41 ± 25.6 months (6–116).	Compared with the previous period, after the start of colistin treatment, significant differences were found in: <ul style="list-style-type: none"> <li>• Mean decline in FEV<sub>1</sub> was slower.</li> <li>• Mean decline in FVC was slower.</li> <li>• Improvement in patient-reported quality of life using a visual analogue scale.</li> <li>• Three patients showed clearance of <i>Pseudomonas</i> spp. at the end of the study period.</li> </ul>	No resistance to colistin was recorded among the bacterial isolates obtained. Patients in the cohort reported no side effects. One patient ceased colistin because of perceived ineffectiveness.
Dhar, R United Kingdom 2010 <sup>53</sup>	Retrospective.	To assess the efficacy of nebulized colomycin in <i>P. aeruginosa</i> -colonized bronchiectasis patients.	Patients with bronchiectasis colonized by <i>P. aeruginosa</i> who had received a minimum of 6 months of treatment. Patients who received concomitant prophylactic macrolide treatment for >4 weeks were excluded.	19 patients 53% women Mean age: 66 years.	Nebulized colomycin 1–2 MU twice daily Mean duration: 21.2 months (6–39).	After initiation of colomycin, there was a significant reduction in: <ul style="list-style-type: none"> <li>• Exacerbations/year.</li> <li>• Hospitalizations/year.</li> <li>• Sputum <i>P. aeruginosa</i> positivity/year.</li> <li>• Sputum volume.</li> </ul>	NS
Berlana, D Spain 2011 <sup>54</sup>	Prospective, observational cohort study.	To compare clinical and microbiologic outcomes in non-CF patients with <i>P. aeruginosa</i> bronchial colonization who were receiving nebulized colistin or colistin + tobramycin with those who were receiving tobramycin alone.	Patients with bronchiectasis or COPD with chronic <i>P. aeruginosa</i> bronchial colonization who were receiving long-term inhaled antibiotic (minimum 12 weeks) with colistin and/or tobramycin, between January 2004 and December 2008. Patients with treatment adherence lower than 80% were excluded.	81 patients with 97 courses of inhaled antibiotic: colistin (n=31), colistin + tobramycin (n=16) or tobramycin (n=50). <ul style="list-style-type: none"> <li>• 86% bronchiectasis</li> <li>• 14% COPD</li> </ul> 45% women Age: 62.5 ± 14.3 years.	Nebulized colistin 1–2 MU every 12h and/or tobramycin 100–200 mg every 12h. Duration: 577.9 ± 470.1 days.	No significant differences between colistin and tobramycin were found in the mean number of hospital admissions, duration of hospitalizations, duration of antibiotic treatment, mortality, or emergence of other opportunistic microorganisms. Patients treated with both inhaled antibiotics had significantly fewer days of hospitalization and fewer days of antibiotic use than those treated with tobramycin alone.	Emergence of resistance to colistin was lower than resistance to tobramycin. The overall frequency of adverse events was 40% (30.3% as probable and 9.8% as definite), mainly respiratory. Events leading to discontinuation in 18% (colistin 26%, tobramycin 13%). No significant differences between colistin and tobramycin were found in adverse events.

<b>Tabernero Huguet, E Spain 2015</b> <sup>59</sup>	Prospective, controlled, open label study.	To assess the effectiveness of inhaled colistin in reducing hospital readmissions in elderly patients with bronchiectasis and chronic bronchial <i>P. aeruginosa</i> infection.	Elderly patients (>65 years) with bronchiectasis, in whom at least one month after admission and correct treatment with two intravenous antibiotics for 15 days, <i>P. aeruginosa</i> isolation persisted in culture with the stable patient. Patients with dementia, or associated terminal illness, were excluded.	38 patients: <ul style="list-style-type: none"> <li>• 19-patient control group: treatment optimization + comprehensive (standardized education and respiratory physiotherapy).</li> <li>• 19-patient intervention group: in addition to the above, inhaled colistin.</li> </ul> Women: 22% (control group) and 15% (intervention group). Mean age: 78.1 years (control group); 77.7 years (intervention group).	Nebulized colistin 1 MU every 12h with i-neb nebulizer. Duration: 1 year.	There were no differences in the annual number of hospital admissions between the control group and the colistin group, or in the length of the hospitalization. There were no differences in lung function or clinical symptoms between both groups. <i>P. aeruginosa</i> was eradicated in 45% of the intervention group, and in only one of the control groups (P<0.05).	No significant changes were observed in <i>P. aeruginosa</i> antibiotic sensitivity or in sputum flora. Five patients (25%) stopped the nebulized treatment because of adverse effects.
<b>Bruguera-Avila, N Spain 2017</b> <sup>61</sup>	Retrospective	To analyze whether the introduction of nebulized colistin in patients with COPD and infection with <i>P. aeruginosa</i> is associated with a decrease of the number and duration of severe exacerbations.	Patients with severe COPD (FEV <sub>1</sub> <50%), frequent exacerbations and chronic/intermittent bronchial colonization by <i>P. aeruginosa</i> who received nebulized colistin for at least 3 months, between January 2010 and December 2014. Patients with asthma, malignancy, unstable heart disease, or a main diagnosis of bronchiectasis were excluded.	36 patients (75% had bronchiectasis). 0% women. Age: 72.7 ± 2.1 years.	Nebulized colistin 1 MU every 12h with i-neb nebulizer. Duration: 10.7±4.2 months.	After initiation of colomycin, there was a significant reduction in: <ul style="list-style-type: none"> <li>• Number of admissions.</li> <li>• Duration of admissions.</li> <li>• These results were similar in patients with and without bronchiectasis.</li> </ul> No pre-post differences were detected in the number of moderate exacerbations not requiring admission. Eradication of <i>P. aeruginosa</i> in 38.9% of patients.	No differences in the culture results during follow-up were found between patients with and without bronchiectasis. Resistance to colistin was only reported in bacteria known as constitutively resistant. Four patients reported bronchospasm (11.1%) and three of these dropped out for this reason (8.4%).
<b>Blanco-Aparicio, M Spain 2019</b> <sup>55</sup>	Prospective, observational cohort study.	To evaluate the efficacy of an antibiotic eradication protocol for <i>P. aeruginosa</i> infection consisting of the administration of systemic antibiotics followed by inhaled colistin for 12 months in patients with NCFB.	Patients with bronchiectasis, ≥1 positive culture for <i>P. aeruginosa</i> , follow-up for at least 1 year after eradication treatment. Patients without systemic antibiotic treatment (oral or IV) prior to starting inhaled antibiotic, and those who achieved successful <i>P. aeruginosa</i> eradication only with systemic antibiotic treatment, were excluded.	67 patients. Women: 40.3%. Age: 67.2 ± 14.6 years.	Eradication protocol: <ul style="list-style-type: none"> <li>• Oral ciprofloxacin (750 mg twice daily) for 3 weeks OR IV tobramycin (5 mg/kg) plus beta-lactam antipseudomonal antibiotics for 2 weeks.</li> <li>• - Nebulized colistin 1 MU every 12h with i-neb nebulizer, for 1 year.</li> </ul>	After initiation of colistin, there was a significant reduction in: <ul style="list-style-type: none"> <li>• Number of exacerbations.</li> <li>• Number of hospital admissions.</li> <li>• Number of antibiotic cycles.</li> </ul> Eradication of <i>P. aeruginosa</i> was achieved in: 61.2% after 3 months; 50.7% after 6 months; 43.3% after 9 months; 40.3% after 1 year. No significant differences in the eradication rate of <i>P. aeruginosa</i> in the short or long term, depending on the number of previous positive sputum cultures.	Mild adverse effects (cough and/or wheezing) were reported by five (7.5%) patients during the first month of treatment but did not result in discontinuation of therapy.

(Continued)

Table 3 (Continued).

First Author Country Publication Year	Type of Study	Objectives of the Study	Inclusion Criteria	Number and Characteristics of Patients Included	Dose and Duration of the Inhaled Treatment	Efficacy / Effectiveness Results	Antibiotic Resistance and Safety Results
López-Gil, MM Spain 2019 <sup>56</sup>	Retrospective	To evaluate whether treatment with nebulized colistin for at least 6 months reduces the number of admissions and visits to the emergency department.	Patients with bronchiectasis with CBI by <i>P. aeruginosa</i> , who had received inhaled colistin for at least 6 months. Patients with lung transplant or interstitial lung disease were excluded.	44 patients. Women: 45.5%. Age: 71.4 ± 11.3 years.	Nebulized colistin 1 MU every 12h with i-neb nebulizer. Duration: 18.27 months.	After initiation of colistin, there was a significant reduction in: <ul style="list-style-type: none"> <li>• <i>P. aeruginosa</i> positive cultures.</li> <li>• Number of antibiotic cycles and days of antibiotic treatment.</li> <li>• Number of emergency room visits, admissions, and hospitalization days.</li> </ul>	There was a slight (not significant) tendency to isolate microorganisms other than <i>P. aeruginosa</i> during treatment, especially <i>S. aureus</i> . 90.9% of patients did not experience any adverse effects attributable to nebulized colistin.
Montón C et al Spain 2019 <sup>63</sup>	Retrospective	To establish whether a combination of nebulized colistin plus continuous azithromycin in severe COPD patients with CBI due to <i>P. aeruginosa</i> reduces the frequency of exacerbations, and to assess its microbiological effect.	Patients with severe COPD and chronic bronchial infection by <i>P. aeruginosa</i> treated with nebulized colistin for at least 3 months between 2005 and 2015, in combination with long-term oral azithromycin. Patients with a main diagnosis of bronchiectasis were excluded.	32 patients (78% had bronchiectasis). Women: 0% Age: 74.7 ± 7 years.	Nebulized colistin 1–2 MU every 12h with Jet nebulizer or 0.5–1 MU every 12h with I-neb nebulizer. Median duration: 17 months (7–24).	Comparing the 24 months prior to the start of treatment with the subsequent 24 months, the following were observed: <ul style="list-style-type: none"> <li>• Reduction in COPD exacerbations (38.3%), hospitalizations (41.5%), and days of admission (41.9%).</li> <li>• <i>P. aeruginosa</i> sputum isolates in both exacerbations and stable phase.</li> <li>• - Eradication of <i>P. aeruginosa</i> in 47% of patients in the first year of follow-up; 28% patients remained negative after two years.</li> </ul>	<i>P. aeruginosa</i> sputum isolates were multidrug-resistant to antibiotics in 43.7% of the patients at baseline; this percentage did not increase throughout follow-up. No resistance to colistin was observed. 3 patients (9%) presented bronchospasm as a late adverse event (after the first 3-month period of treatment).

<b>Martínez-García, MÁ</b> <b>Spain</b> <b>2020</b> <sup>67</sup>	Multi-center study of historic cohorts.	<ul style="list-style-type: none"> <li>To identify the efficacy and safety of treatment with inhaled antibiotics in a dry powder formulation.</li> <li>To identify the patient profile most susceptible to adverse effects and withdrawal of the treatment.</li> </ul>	Patients with bronchiectasis who had received at least one dose in a dry powder formulation. There were no criteria for exclusion due to the intention to perform a real-life study.	164 patients from 33 centers: 86% were treated with colistin and 14% with tobramycin. Women: 53% Age: 65.7 ± 14.4 years.	Dose: NS Duration: 6 ± 6.5 months (1–30).	After initiation of colistin, there was a significant reduction in: <ul style="list-style-type: none"> <li>The number of non-severe and severe exacerbations.</li> <li>Percentage of patients with CBI due to <i>P. aeruginosa</i> (81% vs 52%) and other PPM (29% vs 10%).</li> </ul> No differences were found in sputum production, dyspnea severity, or lung function impairment. There were no statistically significant differences between the efficacy of colistin and tobramycin.	At least one adverse effect was observed in 54.2% of the patients, and 24.4% had to interrupt their treatment as a result of an adverse effect (cough in 84% of these cases). These patients had more severe bronchiectasis, more time of symptoms, previous coughing, more difficulty in handling the device, and less therapeutic education about use of the device. Patients with colistin presented a lower proportion of withdrawals from treatment, less difficulty in using the device, and a smaller proportion of resistances to <i>P. aeruginosa</i> than patients under tobramycin treatment.
<b>de la Rosa-Carrillo, D</b> <b>Spain</b> <b>2021</b> <sup>64</sup>	Multicenter, retrospective cohort study.	To describe the effectiveness and safety of inhaled antibiotics in COPD patients, as well as the patient profile in which they are usually prescribed and the patient groups that can most benefit from this treatment.	COPD patients who had received at least one dose of any inhaled antibiotic treatment in the five years prior to their inclusion in the study (2013–2018), and for whom exacerbation data were available for at least 1 year.	693 patients from 35 centers (73.9% of them had bronchiectasis). Different treatments: colistin (82.5%), tobramycin (15.3%), ceftazidime (1.6%), gentamicin (0.4%), or amikacin (0.1%). Women: 13.7% Age: 74.1 ± 8.5 years.	Dose: NS Median treatment duration: 8.9 months (0.1–71.5).	After initiation of inhaled antibiotics, there was a significant reduction in: <ul style="list-style-type: none"> <li>Number of exacerbations (–33.3%), hospital admissions (–33.3%), and hospitalization days (–26.2%).</li> <li>Frequency and purulence of expectoration.</li> <li>Isolation of any PPM.</li> <li>CBI by any PPM.</li> <li>- CBI by PA.</li> </ul>	25.4% of patients presented non-severe side effects, the most frequent of these being bronchospasm (10.5%), dyspnea (8.8%), and cough (1.7%).

**Abbreviations:** CBI, chronic bronchial infection; CF, cystic fibrosis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; IV, intravenous; MU, mega units; NS, not specified; PPM, potentially pathogenic microorganism; RR, relative risk.

it was well tolerated. These results were encouraging in this severely affected patient group and, according to the authors themselves, strengthened the need for a prospective, adequately powered, randomized controlled trial to investigate the effectiveness of this treatment more fully.

Since then, most of the observational studies on this subject have been carried out by groups of researchers from Spain. Berlana et al<sup>54</sup> carried out a prospective, observational cohort study comparing the clinical and microbiological outcomes of treatment with nebulized colistin compared with those of various tobramycin regimens in 81 patients with bronchiectasis and PA colonization. The results with colistin were similar to those with tobramycin, as regards the mean number of hospital admissions, duration of hospitalizations, duration of antibiotic treatment, adverse events, mortality, and emergence of other opportunistic microorganisms. However, the combined use of colistin and tobramycin appeared to be associated with fewer days of hospitalization and shorter duration of antibiotic treatment.

Another clinical question regarding the use of inhaled antibiotics is their potential ability to achieve the eradication of colonizing PPMs from the airways, thus implying a reversal of the unfavorable clinical course entailed in CBI. In order to analyze the eradication rate of PA from the sputum of bronchiectasis patients treated with inhaled colistin, Blanco-Aparicio et al<sup>55</sup> carried out a prospective study on a cohort of 67 patients who underwent a therapeutic protocol that included an initial systemic antibiotic treatment, followed by 1 year of nebulized colistin. They found a high rate of PA eradication (up to 40.3% of patients per year), even in patients with several previous positive cultures. This finding was also associated with a significant decrease in the number of exacerbations and hospitalizations after 1 year of colistin treatment, compared to the previous year. The authors therefore proposed that *Pseudomonas* eradication should be attempted even when PA is present in several samples of sputum.

With the evidence accumulated up to that moment, it could thus be affirmed that nebulized colistin decreases the number and severity of exacerbations and, accordingly, several groups wanted to validate this premise in their own cohorts of patients with bronchiectasis and CBI due to PA who were receiving this treatment. Thus, López-Gil et al<sup>56</sup> carried out an observational, retrospective, and non-interventionist study in 44 patients, which showed that nebulized colistin significantly decreased the number of emergency visits, the frequency and duration of hospitalizations, and the number of positive cultures at 6 and/or 12 months. The treatment was well tolerated in almost all the patients. These results reaffirmed that treatment with nebulized colistin in these cases of severe respiratory disease seems beneficial for the patient, from the clinical and quality-of-life viewpoint.

Both the presence of bronchiectasis and the susceptibility to infections increase with age.<sup>57,58</sup> Therefore, the elderly population with chronic airway disease constitutes a subgroup of patients potentially amenable to receiving long-term antibiotic treatment, but the usefulness and safety of inhaled antibiotic therapy in the elderly population is a controversial issue. In order to assess the effectiveness of inhaled colistin in this population, Taberero Huguet et al<sup>59</sup> carried out a prospective, controlled, and open label study in 39 elderly patients with bronchiectasis and CBI by PA. They compared one group receiving conventional treatment (which included education and physiotherapy training) with another that also received nebulized colistin. Significantly more patients achieved *Pseudomonas* eradication in the colistin treatment group, but there were no benefits in terms of clinical symptoms, lung function, or use of healthcare resources. Moreover, adverse effects were more common in this group (25% stopped the nebulized treatment because of adverse effects). Taking these results into account, it seems clear that further studies are needed to identify factors or subgroups of elderly patients that could be associated with a favorable clinical response to long-term inhaled antibiotic treatment.

Another hot topic in recent years is the association between bronchiectasis and COPD, which can be present in more than 50% of patients with severe COPD.<sup>60</sup> Furthermore, evidence has accumulated in recent years to show that COPD patients have alterations in their lung microbiome that may result in CBI, which is associated with a higher frequency of bacterial exacerbations. This treatable trait is responsible for a true infectious phenotype that requires personalized treatment, with the use of short- or long-term antibiotic treatment in addition to the usual COPD treatment. In this respect, Bruguera-Avila et al<sup>61</sup> carried out a retrospective study in 36 patients with a primary diagnosis of COPD (75% of whom also had bronchiectasis) who had been treated with nebulized colistin for CBI due to PA. This treatment was associated with a strong decrease in the number and duration of hospitalizations, as well as a low frequency of adverse effects. These results persisted when patients with and without bronchiectasis, or with and without persistence of PA, were analyzed separately, indicating that this treatment is effective even in COPD without bronchiectasis, or in cases in

which the PPM cannot be eradicated. These same authors subsequently published an extension of this study in a larger sample of 62 patients, with the aim of describing changes in the bacteriology of sputum in relation to treatment with nebulized colistin.<sup>62</sup> The results showed that there was no linear trend in the proportion of isolate Enterobacteriaceae, Gram-positive cocci, *Haemophilus influenzae*, or fungi. Isolation of Enterobacteriaceae within a year of the initial administration of nebulized colistin was associated with more ambulatory exacerbations. A similarly designed study by Montón et al<sup>63</sup> analyzed 32 patients with severe COPD and CBI due to PA (of whom 78% had bronchiectasis), treated with a combination therapy of nebulized colistin and continuous cyclic azithromycin. This regimen reduced the number of both exacerbations and PA sputum isolates, and once again the rate of side effects was low.

On the basis of the results obtained in these single-center studies, de la Rosa et al<sup>64</sup> published a multicenter retrospective study promoted by the Spanish Society of Pulmonology (SEPAR) to determine whether the results as regards the effectiveness and safety of inhaled antibiotics in COPD patients were similar across the country. Data from 693 COPD patients from 35 centers were analyzed; 71.7% had bronchiectasis, 46.6% presented CBI by PA, and 82.5% were treated with sodium colistimethate. As in the previous studies, there was a significant decrease after a year of treatment in the number and severity of exacerbations, PPM isolates, and bronchial symptoms. There were no differences between patients with or without bronchiectasis, and 25.4% of patients presented non-severe side effects; the results of the different prescribed antibiotics were not compared. In short, all this evidence has encouraged the more frequent inclusion of inhaled antibiotics in the therapeutic regimens of those patients with COPD and CBI, regardless of whether or not they have associated bronchiectasis.<sup>65,66</sup>

Finally, with regard to studies on new forms of administration, the retrospective multicenter study by Martínez-García et al<sup>67</sup> evaluating the effectiveness of dry-powder inhaled antibiotics (DPIA) is worthy of note. It included 164 patients with bronchiectasis, 86% of whom received colistin. The results showed that DPIA significantly reduced the number of exacerbations, the quantity and purulence of sputum, and the isolation of pathogenic microorganisms. There were no statistically significant differences between the efficacy of colistin and tobramycin. Although there were no serious adverse effects, 40% of patients presented cough, especially those with associated COPD.

It must be taken into account that in the observational studies collected in Table 3, an overall number of only 857 patients with bronchiectasis treated with inhaled colistin were included, after the exclusion of patients who did not have bronchiectasis or received other antibiotics. Moreover, most of these patients are from Spain, following the remarkable and historic implementation of the national guidelines for the treatment of bronchiectasis, which promotes the use of inhaled antibiotic therapy in a greater number of clinical situations than other guidelines. Similar studies are therefore needed in other countries to confirm that the effectiveness and tolerance found in Spain can be extrapolated to other geographical areas and other healthcare systems.

## Randomized Controlled Trials

A search in the PubMed and EMBASE databases for randomized controlled trials (RCT) or meta-analyses that include RCTs with the terms in the title or abstract nebulized OR nebulised OR inhaled OR aerosolized OR aerosolised AND colistin OR colistimethate yields 36 studies. These studies present very diverse methodologies (use of colistin alone, colistin associated with other inhaled or intravenous antibiotic treatment, different indications (ventilator-associated pneumonia,<sup>68</sup> pneumonia due to multi-resistant microorganisms,<sup>69</sup> CF,<sup>70</sup> airway infections due to multi-resistant microorganisms,<sup>71</sup> and bronchiectasis<sup>72</sup>), and different outcomes (mortality, clinical aspects, quality of life, exacerbations, and various microbiological aspects). Some meta-analyses (usually mixing RCT and observational studies) show a positive effect of inhaled antibiotics and a lower number of adverse effects than systemic antibiotics for most of these indications (although in some cases, the results are controversial, depending on the study's methodology or the outcome studied). In general, it can be concluded that there was no clear superiority in those regimens that include inhaled colistin compared to those with other inhaled antibiotics, so further studies are recommended.

More than two decades ago, the first RCT was performed to evaluate the effect of inhaled colistin in subjects with CF by comparing it with inhaled tobramycin for 4 weeks twice daily, in 115 patients aged over 6 years. Although both treatments reduced the bacterial load, the tobramycin nebulizer solution significantly improved the lung function of patients with CF chronically infected by PA but colistin did not; however, this was a short-term study (1 month).<sup>73</sup>

In the case of bronchiectasis, colistin is the most widely used inhaled antibiotic in Spain, either alone or in combination with other drugs.<sup>74</sup> Following the various international guidelines, its indications are diverse: the treatment of primary infection by PA and chronic bronchial infection by PA or other microorganisms. However, these same guidelines point out that there is no clear difference between the regimens used with different inhaled antibiotics.<sup>2-4</sup>

Various RCT performed with other inhaled antibiotics (ciprofloxacin,<sup>76-79</sup> tobramycin,<sup>80</sup> and aztreonam<sup>81</sup>) and various types of inhalers or nebulizers<sup>75</sup> have shown conflicting results in patients with bronchiectasis, even with almost identical methodologies. The case of ciprofloxacin from the RESPIRE<sup>76,77</sup> and ORBIT<sup>78,79</sup> programs is paradigmatic. Each of these two programs consisted of two RCTs with identical methodologies, but only one of each pair of studies had positive results, in addition to the pooled analysis.<sup>79</sup> There is no a clear explanation for these conflicting results, but probably the difference in the baseline characteristics, especially those related to the geographical origin, of the included individuals is one of the most accepted. However, the latest meta-analyses of the effectiveness and safety of IA that include RCT indicate a greater efficacy of inhaled antibiotics, confirming the experience in clinical practice of most physicians who use them in an appropriate selection of patients.<sup>82,83</sup> Nevertheless, given the contradictory results mentioned above, the regulatory agencies have not yet approved any inhaled antibiotic for use in patients with bronchiectasis, pending new RCT that ratify their efficacy.

The specific case of inhaled colistin was not an exception. In 2014, the first study in the PROMIS clinical program (a therapeutic program that received FDA qualified infectious disease product and fast track designation for the prevention of pulmonary exacerbations in adults with bronchiectasis) was published to evaluate the efficacy and safety of colistin in the treatment of PA infection.<sup>72</sup> Given this study's negative results in the intention-to-treat population (ITT) (see below), two larger parallel RCT (PROMIS I and PROMIS II) were launched, one of which has already offered very promising results. In all of these studies, the main objective was the time to the first exacerbation (PROMIS) or the number of exacerbations (PROMIS I and II), given the importance of this factor in bronchiectasis and in its prognosis.<sup>84-87</sup> One of the main limitations of these RCTs is the strict inclusion criteria used since usually only those bronchiectasis patients with bronchial infection by *P. aeruginosa* and multiple exacerbations were included. Therefore, the conclusions cannot be generalized to the usual population seen in clinical practice.

### PROMIS Study (<http://www.isrctn.org/> (ISRCTN49790596))

Published in 2014, this was a randomized placebo-controlled trial to assess the efficacy and safety of inhaled colistin in patients with bronchiectasis and CBI by PA.<sup>72</sup> In all, 35 centers from UK, Russia, and Ukraine recruited patients aged at least 18 years, with confirmed bronchiectasis, at least two or more positive respiratory tract cultures for PA in the preceding 12 months, and one more PA cultured from a sputum sample taken at the screening visit.

After 21 days of oral treatment aimed at PA eradication, 144 patients were randomized to receive colistin (1 million IU; n=73) or placebo (0.45% saline; n=71) via the I-neb device, twice a day for up to 6 months. The primary endpoint was the time to the first exacerbation in an ITT population. Secondary endpoints included the time to the first exacerbation based on adherence recorded by the I-neb (per protocol population), PA bacterial density, quality of life (measured by the SGRQ), and safety parameters.

At least one exacerbation was experienced by 49% and 59% of patients during the study in the colistin and placebo groups, respectively, but there were no differences regarding the time to the first exacerbation in the colistin and placebo groups (165 (42) versus 111 (52) days; p=0.11) for the median time (25% quartile).

During the study, 77.1% of patients had an adherence >80% in both groups. It is significant that, at the level of at least 80% of adherence, the median time to the first exacerbation was significantly longer in the colistin group compared to the placebo group (168 (65) versus 103 (37) days, p=0.028).

As regards secondary objectives, evaluated in an ITT analysis, PA density was reduced after four (p=0.001) and 12 weeks (p=0.008), respectively. The total score of the SGRQ was improved after 26 weeks in the colistin group compared to the placebo group (-10.51 (95% CI: -17.87 to -3.14); p=0.006). There was no change in the mean 24-h sputum weight.

It should be stressed that the decrease in PA density and, above all, the significant improvement in the quality of life experienced by the group treated with colistin compared to the placebo group did not result in any improvement in the



time to the first exacerbation. However, although statistical significance was not reached, the net difference between the groups was 54 days, which could be considered clinically significant, whereas patients with good adherence achieved a difference of 65 days (only 11 days more than in the ITT population) – a difference not much greater but statistically significant. This suggests that it is possible that the number of patients included in the study and/or the number of outcomes (exacerbations) observed were low. Moreover, although the study was multicenter, the patients came from only 3 countries (UK, Ukraine, and Russia), which could have influenced the results as it could not be a representative group. For all these reasons and given that, despite the study being statistically negative, colistin offered hope of being a well-tolerated and effective inhaled antibiotic, the PROMIS I and II studies were designed with a larger number of patients.

### PROMIS I Study (Clinicaltrials: NCT03093974)

This is a Phase 3, placebo-controlled, multicenter clinical trial designed to investigate the efficacy and safety of inhaled colistin (colistimethate sodium) in bronchiectasis chronically infected with PA with at least two exacerbations requiring oral or inhaled antibiotics or one exacerbation requiring intravenous antibiotics in the previous 12 months. Patients were randomized to receive twice-daily colistin via I-neb (delivered dose of 0.3mL of 1 MIU in 1mL 0.45% saline) vs placebo (0.3mL 0.45% saline) for 12 months.

The primary endpoint was the mean exacerbation rate over 12 months. Secondary endpoints (all at 12 months) were: time to the first exacerbation, annualized number of pulmonary exacerbation-free days, number of severe exacerbations, quality of life (measured via SGRQ and QoL-B questionnaire), days of absence from work, and PA density in sputum.

Finally, 377 patients from 85 centers in 12 countries (Belgium, Netherlands, Spain, Switzerland, UK, Australia, Germany, Greece, Israel, Italy, New Zealand, Poland, and Portugal) were included, thus increasing the study's representativity and statistical power with respect to the previous one (PROMIS). Patients were randomized – 177 to colistin via I-neb and 200 to placebo. The annual rate of exacerbations was lower in patients receiving colistin vs placebo (0.58 per patient per year vs 0.95, rate ratio (RR) 0.61; 95% CI: 0.46–0.82,  $p=0.001$ ). The effect of the treatment was even greater in adherent subjects (43.5% reduction in exacerbations,  $p=0.0008$ ). Moreover, the time to the first exacerbation was prolonged in the colistin group (HR 0.59, 95% CI 0.43–0.81,  $p=0.00074$ ). Severe exacerbations were also reduced (RR 0.41, 95% CI: 0.23–0.74,  $p=0.003$ ). The quality of life, as measured by the SGRQ, improved significantly in the colistin arm, with 4.55 points of difference vs placebo after 12 months treatment ( $p=0.0055$ ). After 28 days treatment, PA density was significantly reduced in the treatment arm,  $p<0.00001$ .

No further data are available as the study was presented as an abstract at the 2021 European Respiratory Congress<sup>88</sup> and has yet to be published at the time of writing.

### PROMIS-II Study (Clinicaltrials: NCT03460704)

This study, for no data have been published at the time of writing, presents an identical methodology to the PROMIS-I study, although the origin of the patients is different. In this case, the patients come from 12 countries (USA, Argentina, Australia, Canada, France, Germany, Greece, Israel, Italy, New Zealand, Poland, and Portugal).<sup>89</sup>

The need to present positive results in favor of colistin in an ITT population model in both studies with identical methodologies means that the scientific community is waiting expectantly for the results of this second RCT, given that, if it comes out positively in favor of colistin treatment, it may open the door for official approval from the regulatory agencies for its indication in bronchiectasis and bronchial infection due to PA – this would make colistin the first inhaled antibiotic on the market with this indication.

## Safety of Inhaled Colistin

Table 3 (last column) summarizes the main findings on the safety of inhaled colistin in observational studies.<sup>52,54–56,59,61,63,64,67</sup> Some points can be highlighted: 1. From 0% to 40% of patients had at least one side effect while used inhaled colistin. In almost all cases the side effects were mild, being the most frequent cough, bronchospasm and dyspnea; 2. The number of side effects was higher in colistin dry-powder inhalers (54.2%), being the most frequent cough (84%) that caused the interruption of treatment in 24.4% of patients. Risk factors for adverse effects were: more severe bronchiectasis, more time of symptoms, previous coughing, more difficulty in handling the device, and less therapeutic education about use of the device;<sup>67</sup> 3. Very few cases of emerging

resistance of PA to colistin emerged during the studies and was lower than those emerging to tobramycin. In the same lines, no unexpected serious adverse reactions were reported and no colistin-resistant strains of PA or treatment-emergent pathogens were identified in RCTs.<sup>72,88</sup>

## Future Challenges

In the light of all the above, it is evident that several challenges will have to be faced in coming years if inhaled colistin is to earn its place in the therapeutic arsenal of patients with respiratory infections. If the good results of the PROMIS program are confirmed, however, the priority should be to obtain a formal indication from the regulatory agencies for the treatment of CBI due to PA in bronchiectasis.

Further studies (preferably RCT) should also be carried out to increase our knowledge of the effectiveness and safety of inhaled colistin in different clinical situations. Its effect on bronchial infection by PPMs other than PA, such as *S. aureus* or the most common non-fermenting Gram-negative bacilli (*A. xylosoxidans*, *S. maltophilia*, among others), should also be analyzed. Similarly, it is necessary to deepen our knowledge of the effectiveness of colistin on CBI in conditions other than bronchiectasis and CF (eg, COPD and/or asthma). Subsequent studies should also aim to analyze the effects of colistin on primary infection by PA, in terms of its eradication rate, the optimal time to start treatment after the first isolation and the appropriateness of associating it with systemic antibiotic treatment. In this respect, there needs to be further classification of the role of biomarkers and patient genetics and endotypes in identifying the best candidates for this treatment, as well as the evaluation of its maintenance period. Furthermore, the effects of different doses of colistin, and of the nebulized and dry-powder forms, should be assessed, since this information would permit an optimization of its use and perhaps even its tolerance, without losing any effectiveness. The effect of the different inhalation devices should also be prospectively evaluated, even by making direct comparisons between them. Moreover, it would be important to know the effects of colistin on variables other than exacerbations, such as the quality of life, patient-reported outcomes, lung function, and mortality.

Such studies which would fundamentally assess the effectiveness of colistin, but others should also be undertaken to evaluate its long-term adverse effects, such as the generation of antibiotic resistance, the appearance of emerging or multi-resistant microorganisms, or unwanted effects on the lung microbiome, among others.

Inhaled antibiotics in general, and colistin in particular, are drugs whose average price is relatively high, and this factor, together with the lack of their formal indication for patients with bronchiectasis, has made some healthcare providers reluctant to authorize their use. Any future research to determine the effectiveness of this type of treatment should therefore be combined with an analysis of its cost-effectiveness and cost-utility. It is very likely that its use can be shown to reduce the high overall healthcare costs associated with the treatment of bronchiectasis, especially in patients with CBI.<sup>22</sup> This would imply both a benefit for the patient and for the health system, and it would also make it easier to overcome any resistance to financing its treatment.

Going beyond clinical research, there is a need to carry out new pharmacological studies that analyze PK/PD parameters in humans, including the use of inhaled formulations (particularly with new combinations of colistin and other antibiotics) and of colistin with the new nanoparticles that are currently in development.<sup>90,91</sup>

## Conclusions

Nebulized colistimethate sodium is a therapeutic tool that can help improve clinical control in patients suffering from respiratory infections due to PPM, particularly those with resistance or multi-resistance to systemic antibiotics. In recent decades, there has been increasing scientific evidence of the deleterious effect of CBI due to PPM in bronchiectasis patients, coupled with an increasing use of nebulized colistimethate sodium in this type of patient, leading to a growing body of evidence confirming its notable effectiveness and safety. However, it is important to recognize that whilst nebulised colistin is recommended in many guideline documents and in widespread use, there is a paucity of randomized clinical trial data to clearly demonstrate.

## Disclosure

The authors report no conflicts of interest in this work.

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