

# Bronchiectasis in Chronic Obstructive Airway Disease: More than a Comorbidity?

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## ABSTRACT

Beyond the bronchial dilatations associated with age, several studies have documented a higher prevalence of bronchiectasis in patients with severe asthma or chronic obstructive pulmonary disease (COPD). Perhaps COPD or asthmatic patients with bronchiectasis represent a clinical phenotype characterised by greater clinical and functional severity, a higher number of exacerbations and, in the case of COPD, greater colonisation by potentially pathogenic microorganisms and probably a poor prognosis. Although international guidelines recommend that the two diseases are treated separately when they coexist, patients with COPD or asthma associated with bronchiectasis may benefit from specific treatments, such as long-term antibiotics, physiotherapy or macrolides. It is biologically plausible that severe asthma, and especially severe COPD, are related to *de novo* bronchiectasis, but no study has yet demonstrated any cause-effect relationship. Early diagnosis and treatment of bronchiectasis in COPD and asthma could be crucial to improve their prognosis. This relationship poses an interesting scientific challenge for the future. (BRN Rev. 2017;3:178-91)

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## INTRODUCTION

Bronchiectasis can be considered the final stage in the damage to the lung caused by a range of diseases, both respiratory and systemic. The most recent guidelines issued by the Spanish Society of Pneumology (2017) on the diagnosis and treatment of bronchiectasis define it as "*a chronic inflammatory bronchial disease with irreversible dilatation of the bronchial lumen that can have various causes. Clinically, it is usually associated with coughing and chronic expectoration, as well as recurrent exacerbations of an infectious nature. It can coincide with chronic bronchial infection and a progressive decline in lung function; all of this can lead to a deteriorated quality of life and increased morbidity and mortality*" (in press). This definition tends to exclude bronchial dilatations associated with old age and the traction bronchiectasis commonly associated with destructive interstitial processes in the lung and with ruptured anchors in the bronchial wall resulting from pulmonary emphysema; this omission can be explained by the particular characteristics of these disorders (negligible symptoms and lack of any clear inflammatory or infectious substrate that can be evaluated by the degree of bronchial wall thickening)<sup>1</sup>. Several chronic respiratory diseases (usually those with an inflammatory profile) can trigger (or be associated with) bronchiectasis. Two of them in particular have attained special prominence in recent years due to their epidemiological impact: chronic obstructive pulmonary disease (COPD), including alpha-1 antitrypsin deficiency ( $\alpha 1$ -ATD)<sup>2,3</sup> and asthma<sup>4</sup>. However, the associations between COPD/asthma and bronchiectasis are not devoid of controversy, for various reasons. Firstly, these diseases are clinically similar, which means that their diagnosis is often

confused; secondly, they are common diseases and can therefore coexist without any need for a link between them (for example, in a patient with COPD and bronchiectasis in the upper lobes as a result of a previous pulmonary tuberculosis); and, finally, because there is no definitive proof that COPD and asthma cause bronchiectasis *per se*, although this does seem biologically plausible. This review refers exclusively to non-cystic fibrosis bronchiectasis, and will devote special attention to the relationships between bronchiectasis and both COPD and asthma; we shall examine the prevalence of bronchiectasis in patients with COPD or asthma and its degree of association with these diseases, as well as its impact and therapeutic repercussions, and, finally, the challenges facing us in the future.

## BRONCHIECTASIS IN PATIENTS WITH COPD

### Prevalence

Bronchiectasis is a complex and heterogeneous disease that is ideally suited for precision medicine because it likely represents a continuum of different diseases that may share biological mechanisms (often referred to as "endotypes") and present similar clinical and prognostic (often referred to as "phenotypes") that require an individualized therapeutic approach based on the identification of treatable traits in each patient<sup>5</sup>. The gold standard for diagnosing bronchiectasis is high-resolution computed tomography (HRCT) of the chest. There are various criteria for a radiological diagnosis, the most used probably being the Naidich criteria, based on a broncho-arterial ratio  $> 1$ , a lack of tapering on the

periphery of a bronchus and the existence of dilated bronchia less than 1 cm from the parietal or mediastinal pleura<sup>6</sup>. However, any definition of bronchiectasis as an airway disorder requires a compatible clinical picture (usually productive cough). In this respect, bronchiectasis associated with interstitial lung disease ("traction bronchiectasis") or dilated bronchia typical of the elderly should not be considered "true" bronchiectasis<sup>1</sup>. Moreover, bronchiectasis is usually associated with bronchial wall thickening, as a consequence of bronchial inflammation. Some authors have considered bronchiectasis without a compatible clinical picture to be "dry bronchiectasis". It is important to stress that the presence of a spirometric pattern of airway obstruction (forced expiratory volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC) < 0.70) is not essential for a diagnosis of bronchiectasis (in contrast with COPD), even though this is the functional pattern most frequently seen in bronchiectasis<sup>7,8</sup>.

If we accept the broad definition of bronchiectasis as abnormal bronchial dilatations, then there are no reliable data on its prevalence in patients with COPD. Depending on the methodology used in the various studies to date, the reported prevalence ranges from 2 to 72%<sup>9-24</sup>. Table 1 shows some of the common causes of an under- or overestimation of the presence of bronchiectasis in patients with COPD. Overestimations are probably more frequent, largely due to: the inclusion of patients in a severe or exacerbatory phase; the appearance of dynamic bronchial dilatations typical of patients with COPD; the selective application of HRCT; asymptomatic bronchiectasis related to (or confused with) emphysema; and the presence of bronchial dilatations typical of the elderly (reported in up to 20% of individuals aged above

**TABLE 1.** Reasons for the discrepancies observed in the various studies of the prevalence of bronchiectasis in patients with chronic obstructive pulmonary disease

Inclusion of bronchiectasis of any aetiology, not only that of unknown origin
Inclusion of non-consecutive COPD patients
Non-consecutive performance of HRCT
Bronchial dilatations due to old age
Dynamic bronchial dilatations secondary to COPD
Inclusion of patients with COPD only in an exacerbation phase
Inclusion of traction bronchiectasis (e.g., secondary to emphysema or interstitial disorders)
Performance of HRCT with an objective other than the diagnosis or impact of bronchiectasis (e.g., quantification of emphysema)
Diagnostic errors (e.g., emphysema, pulmonary cysts)
False bronchiectasis in cases of hypoxic vasoconstriction
Lack of identification in pulmonary hypertension
CT without high-resolution algorithms
Inclusion of patients with bronchiectasis in only one segment of the lung

COPD: chronic obstructive pulmonary disease; CT: computed tomography; HRCT: high-resolution computed tomography.

60-65 years). It must not be forgotten however, that there are other reasons for underestimating the presence of bronchiectasis: the use of computed tomography (CT) without high-resolution algorithms, or of HRCT for purposes other than evaluating the presence of bronchiectasis, such as quantifying emphysema<sup>3,25,27</sup>.

It is possible that the most reliable evaluation of the prevalence of bronchiectasis in COPD patients from the seventeen, methodologically diverse, studies published to date should focus on those with the most appropriate methodology (albeit not entirely free of problems): an objective to evaluate bronchiectasis of unknown origin in consecutive COPD patients in a clinically stable phase who all underwent a prospective HRCT scan. These criteria are

**TABLE 2.** Studies designed to evaluate bronchiectasis of unknown origin in consecutive COPD patients in a clinically stable phase who all underwent a prospective high-resolution computed tomography (HRCT) scan

Author (yr)	n	COPD	Study design	Bronchiectasis criteria	Bronchiectasis prevalence	Lower lobes
Patel et al. (2004)	54	Moderate-to-severe	Prospective	Naidich	<b>50%</b>	66.7%
Martinez-García et al. (2011)	92	Moderate-to-severe	Prospective	Naidich	<b>57%</b> 34.7% in moderate 72.5% in severe	60.4%
Arram OA et al. (2012)	69	Moderate-to-severe	Cross-sectional	Naidich	<b>47.8%</b> 31.1% moderate 62.2% severe	67%
Stewart JI et al. (2012)	3752	GOLD II-IV	Prospective	Visual assessment	<b>20.8%</b> 18.8% GOLD II 24% GOLD III-IV	--
Martinez-García et al. (2013)	201	Moderate-to-severe	Prospective	Naidich	<b>57.2%</b>	81%
Tulek (2013)	80	All stages	Cross-sectional	Naidich	<b>33.8%</b> 40% in moderate-to-severe	--
Doria et al. (2016)	65	All stages	Retrospective	Bhalla	<b>33.8%</b>	--

COPD: chronic obstructive pulmonary disease; GOLD: global initiative for chronic obstructive lung disease.

satisfied by the seven studies<sup>9,12,14-16,20,23</sup> in table 2, which gives us a narrower range of prevalence: 20.8-57.2%. Another significant finding is the positive linear association between the degree of severity of COPD and the prevalence of bronchiectasis, which is around 50% in severe cases, a higher figure than that found in healthy elderly people. The bronchiectasis found in COPD is usually cylindrical, situated in the base of the lungs and accompanied by thickening of the bronchial wall resulting from the inflammation associated with both diseases.

## What are the characteristics of patients with associated COPD and bronchiectasis?

On the assumption that the two diseases are associated, beyond any overlapping prevalence due to the synchronic appearance of

bronchiectasis for other reasons, patients with this association present several characteristics that differentiate them from COPD patients with no bronchiectasis. These differences are not limited to clinical factors but also involve functional, microbiological, inflammatory and even prognostic and therapeutic factors, which has led some authors to conclude that there is a specific clinical phenotype of COPD patients with bronchiectasis. Table 3 shows the results of the two meta-analyses published to date<sup>28,29</sup>. Patients with COPD associated with bronchiectasis present a lower value of post-bronchodilatory FEV<sub>1</sub> and a higher probability of severe airway obstruction.

Of all these factors, perhaps the one most consistently reported is the presence of greater expectoration than usual; a higher number of exacerbations; a higher probability of chronic colonisation by potentially pathogenic microorganisms (PPM). As we shall see below,

**TABLE 3.** Comparison between patients with COPD with and without bronchiectasis in two meta-analyses published in this respect

	Du et al. (2016) <sup>25</sup> 14 studies (n = 5,329)	Ni et al. (2015) <sup>24</sup> 6 studies (n = 881)
Bronchiectasis prevalence	29%	54.3%
<b>General characteristics</b>		
Males	–	OR: 1.62 (1.15-2.28); p = 0.006
Age	–	WMD: 1.8 years (0.05-3.55; p = 0.04)
Smoking history	–	WMD: 4.63 pack-years; 1.61-7.65; p = 0.003
<b>Clinical parameters</b>		
More daily sputum production	–	OR: 2.30 (1.66-3.19; p < 0.00001)
More exacerbations (previous year)	OR: 1.97 (1.29-3)	WMD: 1.54 (0.56-2.53; p = 0.002)
<b>Lung function</b>		
Lower FEV <sub>1</sub> /FVC ratio	–	WMD: -8.05% (-10.65 to -5.45)
Lower post-bd FEV <sub>1</sub> predicted severe airflow obstruction	OR: 1.31 (1.09-1.58)	WMD: -11.06 (-18.27 to -3.85)
<b>Systemic inflammatory markers</b>		
CRP level	--	WMD: 6.11 (0.26-11.95)
Albumin level	--	WMD: -0.14 (-0.23-0.06)
<b>Microbiological profile</b>		
Chronic PPM colonisation	OR: 3.76 (2.37-5.96)	OR: 7.33 (4.61-11.67)
Isolation <i>P. aeruginosa</i>	OR: 4.75 (1.25-18.04)	OR: 3.59 (1.89-6.47)
<b>Prognostic parameters</b>		
Mortality	OR: 1.96 (1.04-3.70)	

Data are presented as Odds Ratio or Weighted Mean Difference (WMD); CRP: C-Reactive Protein; PPM: Potentially Pathogenic Microorganisms; odds ratio (OR) or weighted mean difference (WMD).

CRP: C-reactive protein; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; post-bd: post bronchodilator test; PPM: potentially pathogenic microorganisms.

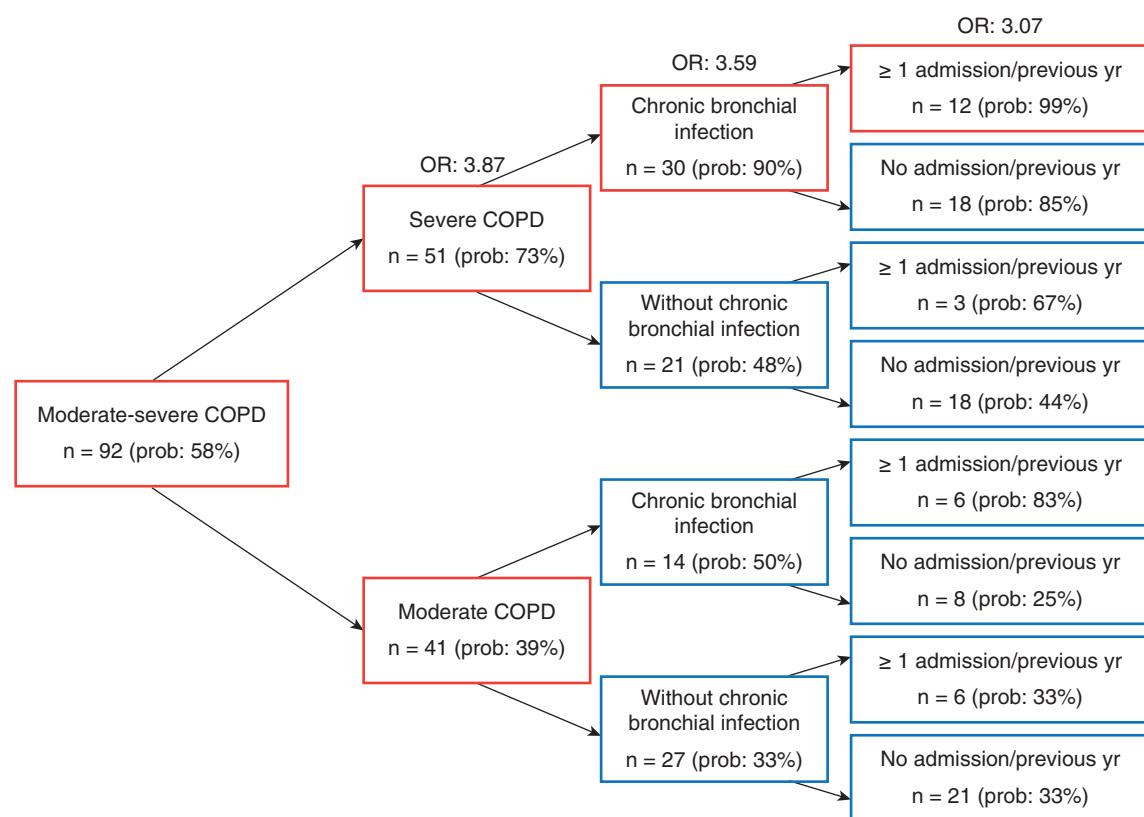
this concurs with the hypothesis that greater inflammation and chronic bronchial infection are a possible cause of this bronchiectasis. Along these lines, one study found that the probability of bronchiectasis in patients with severe COPD, chronic colonisation by PPM and multiple exacerbations was three times higher than that in patients without these characteristics (Fig. 1)<sup>20</sup>.

## Prognostic impact of bronchiectasis

The presence of bronchiectasis has a marked impact on the vital prognosis of patients with COPD. Four studies have analysed this

phenomenon to date. Of these, three found an increase in mortality (OR's between 2.15 and 3.96) after adjustment for different confounders (15, 30, 31) but the fourth did not (odd ratio (OR): 1.05)<sup>18</sup>. A recent meta-analysis concluded that COPD patients with bronchiectasis present double the mortality after adjustment for age, gender, body mass index and pulmonary function (adjusted OR: 1.96; 95% CI: 1.04-3.70), but the studies in question were extremely heterogeneous and new ones are required to confirm this relationship<sup>29</sup>.

There has only been one study analysing the impact of bronchiectasis on the quality of life



**FIGURE 1.** Variables associated with a greater prevalence of bronchiectasis in patients with COPD.

In red, COPD patients with high probability of presenting bronchiectasis.

COPD: chronic obstructive respiratory disease; OR: odds ratio; prev: prevalence; prob: probability; yr: year.

in patients with COPD. Tan et al.<sup>24</sup>, using the COPD Assessment Test (CAT) to evaluate quality of life, concluded that those patients with COPD and bronchiectasis had 1.89 (1.36-2.36;  $p < 0.0001$ ) more probability of having a CAT score  $\geq 10$  than those without bronchiectasis, after adjusting by age, sex, body mass index, FEV<sub>1</sub> and pack years.

Finally, one of the most consistently evident factors is the propensity of patients with bronchiectasis-associated COPD to have not only more exacerbations<sup>14-17</sup> but also ones that are more severe<sup>13,15,17,20</sup> and longer-lasting<sup>9</sup>,

although not all authors have found this association<sup>18,19,24</sup>. Taken together, however, both the meta-analyses<sup>28,29</sup> found a relationship between exacerbations and bronchiectasis (Table 3).

## Therapeutic implications

The degree of scientific evidence for the various treatments commonly used in patients with COPD and/or bronchiectasis is very inconsistent. In the case of COPD, the various short- and long-term bronchodilators and their combinations have been most widely documented,

while in the case of bronchiectasis prolonged antibiotic treatment for chronic bronchial infection by *P. aeruginosa* and macrolides have been most fully studied (although bronchial dilators are extensively used in these patients, there has been little research on this topic). Respiratory rehabilitation is strongly supported by scientific evidence in both diseases, and this could be particularly effective in patients with both COPD and bronchiectasis, but treatments such as chromones, mucolytics, anti-leukotrienes and other anti-inflammatory drugs have barely been documented for either disease. Finally, there are other treatments, such as inhaled steroids, that are widely used but are still subject to great debate, so there is a tendency to prescribe them only on an individual basis<sup>7,8,32,33</sup>.

Regardless of the type of relationship between COPD and bronchiectasis in a specific patient with both diseases at the same time, it is widely agreed that the two diseases must be treated separately, as indicated by the international guidelines for both COPD and bronchiectasis<sup>7,8,32,33</sup>. There are some specific circumstances that need to be taken into account, however:

**Inhaled steroids.** Some authors have observed that the use of inhaled steroids in COPD patients can lead to an increased incidence of pneumonia and other infections<sup>34</sup>. It therefore seems logical to suppose, despite the lack of any corroboratory scientific evidence – an interesting study would surely be welcome –, that care must be taken with inhaled steroid treatment in patients with not only COPD but also bronchiectasis, especially in situations of chronic bronchial infection by PPM. Inhaled steroids should be taken at minimum dose possible. One small clinical trial concluded that it is possible to decrease the dose

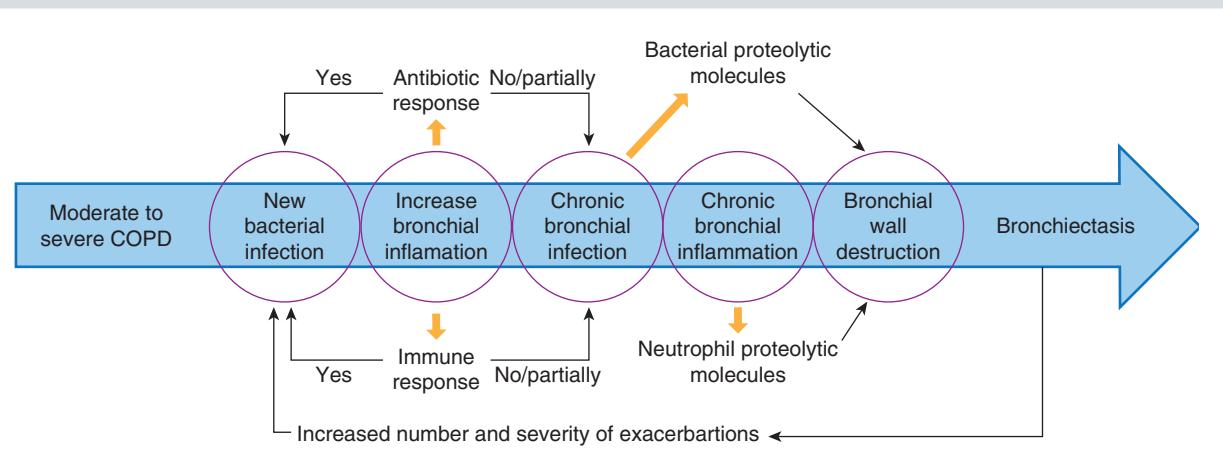
of inhaled steroids (if the patient needs this treatment), combining it with long-acting beta 2 bronchodilators<sup>35</sup>.

**Macrolides.** Macrolides at immunomodulatory doses have been shown to significantly reduce the number of exacerbations in patients with bronchiectasis<sup>36-38</sup>, and also, to a lesser extent, in patients with COPD<sup>39</sup>; his treatment could therefore be of special interest to those patients with both diseases, particularly when they involve multiple exacerbations. Other anti-inflammatory therapies such as phosphodiesterase 4 inhibitors may also be useful in this particular phenotype of patients.

**Long-term inhaled antibiotics.** Another interesting question is the possible prophylactic use of inhaled antibiotics in these patients in situations of chronic bronchial infection by PPM. These drugs are already widely used in patients with bronchiectasis (of all aetiologies), often with good results<sup>40,41</sup>, but there is barely any scientific evidence available regarding their use in COPD patients<sup>42</sup>. It is possible, however, that their administration in patients with COPD (outside any exacerbation period) and chronic bronchial infection (even without bronchiectasis) could represent an interesting line of research when it comes to evaluating these patients' progress, as well as avoiding the adverse effects and problems associated with the administration of systemic antibiotics.

## Is COPD-bronchiectasis a special phenotype of COPD patients?

As mentioned above, the evidence available until now seems to indicate that the presence of bronchiectasis in COPD patients leads to



**FIGURE 2.** Pathophysiological hypothesis for the formation of bronchiectasis in patients with COPD.

COPD: chronic obstructive pulmonary disease.

greater clinical severity, more exacerbations, changes in therapeutic handling and possibly a poorer prognosis<sup>28,29</sup>. Deciding whether this information is sufficient to confirm the existence of a differential clinical phenotype is no easy task. On the one hand, it would be desirable to have more scientific evidence on the prognostic implications of bronchiectasis and the stability of this possible new phenotype over time; on the other hand, we need some better designed studies that analyse more homogeneous groups of patients. Nevertheless, this group of patients is already worthy of investigation, particularly as there is a theoretical possibility of preventing this association. As bronchiectasis due to COPD can occur in patients with previous chronic bronchial infection from PPM (which we could call the infectious phenotype), it is not far-fetched to suppose that treatment of this chronic infection could prevent the appearance of irreversible alterations (bronchiectasis) to the bronchial lumen. This theoretical infectious (or bronchiectatic) phenotype may be closely related to the well-known chronic bronchitis<sup>43</sup>

and exacerbator phenotypes of COPD<sup>44</sup>. Clinical studies are required in patients with COPD and chronic bronchial infection, using drugs such as inhaled antibiotics to confirm their efficacy in eradicating these microorganisms and, above all, improving these patients' evolution. Studies of biomarkers and genetics are also needed to answer questions such as: Why do not all COPD patients develop chronic bronchial infection? And why do not all patients with chronic bronchial infection develop bronchiectasis?

## Causal relationship

Although it is a fact that most aetiological tables for bronchiectasis include COPD and asthma, no study has yet demonstrated any cause-effect relationship. Nevertheless, this is biologically plausible (Fig. 2). The appearance of a bacterial infection in patients with COPD (especially in its severest forms) will produce greater bronchial inflammation<sup>45</sup>. This situation, which can be perpetuated over time,

is very likely to lead to more exacerbations<sup>46</sup>. In cases of exacerbation both the antibiotic treatment administered and the host immune system will often manage to eradicate the bacteria, or at least significantly reduce the number of colonies. When this does not occur, however, there may be chronic bronchial infection by PPM<sup>47</sup>. It has been known since the 1980s, through the pathogenic vicious circle described by Cole<sup>48,49</sup>, that this is the most common gateway to bronchiectasis resulting from chronic inflammation; to the production of proteolytic molecules by both bacteria and the neutrophils themselves; to the destruction of local defence systems and, therefore, the perpetuation of bronchial infection; and, finally, to the destruction of the bronchial wall, along with the dilatation of the bronchial lumen typical of bronchiectasis. Anyway, since a cause-and-effect relationship between COPD and bronchiectasis is still a hypothesis, we always have to rule out any cause of bronchiectasis in a COPD patient with bronchiectasis, as some guidelines have clearly stated, making all the complementary tests and collecting the specific clinical history in order to discover an alternative aetiology. It is only when an alternative aetiology does not exist that we can think of the possibility that this bronchiectasis has been caused by COPD itself.

Going beyond any pathophysiological hypothesis, there is a need to demonstrate “de novo” bronchiectasis in COPD patients that is not due to any other aetiologies in order to evaluate any possible causal relationship. This requires longitudinal studies with multiple HRCT over a period of time as well as investigation of the variables associated with the creation of new bronchiectasis, or the growth of pre-existing bronchiectasis. The

basic problem with such studies is the possibility of a very prolonged timeframe (i.e., years) for any development of bronchiectasis.

## Future challenges

The COPD-bronchiectasis phenotype, also known as the bronchiectasis-COPD overlap syndrome (BCOS), still poses an interesting scientific challenge<sup>50</sup>, as the studies performed today indicate that this is a special clinical subgroup of patients that could experience therapeutic and prognostic repercussions and could therefore, in the not too distant future, give rise to the development of specific drugs. Table 4 shows some of the interesting challenges posed by this association, some of which have already been discussed above.

## Bronchiectasis and emphysema

There is very little information available about the relationship between emphysema (in the context of a patient with COPD not due to  $\alpha$ 1-ATD) and bronchiectasis. It is well known that patients with significant emphysema can present traction bronchiectasis with few characteristic symptoms and little thickening of the bronchial wall. Beyond this, however, the two diseases can, to some extent, share a similar production mechanism (an imbalance between proteases and antiproteases), which makes their possible relationship worthy of investigation. Fugimoto et al.<sup>51</sup> studied the radiological phenotype of 172 COPD patients and found that more than 25% presented a combination of emphysema and bronchial wall thickening. These patients, compared to those in whom it was possible to identify only

**TABLE 4.** Future challenges in the relationship between bronchiectasis and COPD

What is the real prevalence of bronchiectasis in COPD patients?
What is the prognostic impact of the presence of bronchiectasis in COPD patients?
Are the usual radiological criteria for bronchiectasis valid in COPD patients?
What is the role of exacerbations and chronic bronchial infection by PPM?
Is COPD-bronchiectasis a different phenotype from COPD?
Is COPD capable of triggering bronchiectasis?
Is bronchiectasis a mere comorbidity or just a phase in the natural history of a COPD?
In which COPD patients should the presence of bronchiectasis be ruled out?
Which pathophysiological mechanisms associate COPD with bronchiectasis?
How come not all COPD patients present bronchiectasis?
How come not all COPD patients present chronic bronchial infection by PPM?
What are the predictive biomarkers of bronchiectasis?
What is the role of anti-inflammatory drugs (macrolides or phosphodiesterase 4 inhibitors) in these patients?
Do inhaled steroids have a deleterious effect on these patients?
What are the role and indications of inhaled antibiotics?
What role does the modification of the microbiome play in these patients?
What is the pathophysiological association between bronchiectasis and $\alpha 1$ -ATD?
Does inhaled and intravenous augmentation therapy help both emphysema and airway disease in $\alpha 1$ -ATD?
What are the prevalence and impact of emphysema in bronchiectasis?
Should a future therapeutic approach target both components?

$\alpha 1$ -ATD: Alpha-1 antitrypsin deficiency; COPD: Chronic obstructive pulmonary disease; PPM: Potentially pathogenic microorganisms; ATD: Antitrypsin deficiency.

emphysema, presented a greater number of exacerbations and greater production of sputum. Other authors have studied this association in the opposite direction. Thus, Loubeyre et al.<sup>52</sup> found radiological signs of emphysema in 45% of 90 patients with bronchiectasis who

had never smoked. One particularly interesting finding was the appearance of bronchiectasis in the same segments of the lung as emphysema, along with an apparent correlation between the severity of the two diseases. The authors concluded that the emphysema found could be the consequence of the bronchial inflammation present in bronchiectasis, and that there could therefore be a causal relationship. Furthermore, Loebinger et al.<sup>53</sup> observed in 91 patients with bronchiectasis that the presence of emphysema and thickening of the bronchial wall is independently associated with higher mortality (findings similar to those of Tang X et al.<sup>54</sup> in 89 patients with bronchiectasis) and concluded that the presence of emphysema might be a result of inflammation in distal airways in response to the development of bronchiectasis, leading to a deterioration in lung function and a poorer prognosis.

## Bronchiectasis and alpha-1 antitrypsin deficiency and emphysema

$\alpha 1$ -ATD is a genetic condition that predisposes to an early pulmonary emphysema. The prevalence and impact of this airway disease are greater than previously thought. Some reports have suggested an association, even a causal link, between emphysema and bronchiectasis<sup>55</sup>. The prevalence of  $\alpha 1$ -ATD in bronchiectasis is very low<sup>56-58</sup>. Conversely, the frequency of bronchiectasis in  $\alpha 1$ -ATD is difficult to ascertain and varies from one study to another (27-60%). Population-based bronchiectasis registries have not shown any great differences in alpha-1 antitrypsin (AAT) allele frequencies, compared with control populations. The relationship between bronchiectasis and

emphysema has a regional pattern underlying pathogenic processes since the presence of bronchiectasis was greater in lobes in which the emphysema score was higher<sup>59</sup>.

In a study published by Parr et al.<sup>59</sup> in 74 patients with  $\alpha$ 1-ATD (Pi<sup>ZZ</sup>), CT bronchiectasis was found in 70 patients (95%), whilst clinically significant disease, was only detected in 20 patients (27%) being cylindrical bronchiectasis the most common morphological type. There was a correlation between greater bronchiectasis severity and more severe emphysema and between bronchial wall thickening and FEV<sub>1</sub>.

## BRONCHIECTASIS AND ASTHMA

### Prevalence of bronchiectasis in asthmatic patients

Leaving aside allergic bronchopulmonary aspergillosis, whose characteristics include the presence of asthma and central bronchiectasis, several studies have found a greater prevalence of bronchiectasis in patients with asthma (especially when this is severe or difficult to control). When the radiological definition of bronchiectasis is taken as a presence of a broncho-arterial quotient greater than 1, its prevalence is 30-40%. This type of bronchiectasis is usually cylindrical and found in the bases of the lungs, and it is mainly associated with thickening of the bronchial wall that reveals the existence of unresolved bronchial inflammation<sup>60-65</sup>.

### Bronchiectasis and asthma. A pathophysiological hypothesis

Bronchiectasis is traditionally considered to be the result of structural damage caused by

a chronic bronchial infection and subsequent inflammation. It is possible that this is not the only mechanism, however. It seems that while the presence of inflammation (and its consequences) is a condition *sine qua non* for the appearance of bronchiectasis, this is not the case with bronchial infection<sup>49</sup>. Thus, patients with rheumatoid arthritis, or those in the early phases of cystic fibrosis with no bronchial infection, may already present bronchiectasis. As regards asthma (especially in its most severe forms), an analysis of the various studies that have examined the structural bronchial damage in this disease show a clear increase in both the prevalence of bronchiectasis and the thickness of the bronchial wall (as a result of the substantial bronchial inflammation that is usually present)<sup>60-66</sup>. There is no evidence to date, however, of any abnormal isolation of potentially pathogenic microorganisms (although this has not been specifically studied). All in all, it is still not clear to what extent the pathophysiological hypothesis causally linking severe asthma with bronchiectasis is well-founded, or to what extent bronchiectasis is just another comorbidity in these patients. It has also been suggested that there are other mechanisms, such as microaspirations and gastro-oesophageal reflux, that could be intermediary factors between asthma and bronchiectasis.

### Impact of bronchiectasis on asthma

Various authors have observed that bronchiectasis is found in the severest clinical and functional forms of asthma, generally concomitant with predominantly neutrophilic inflammation<sup>60</sup> or emphysema, or with a current or previous smoking habit<sup>64</sup>. Bronchiectasis is

also often seen in long-term, non-allergic asthma<sup>60,64</sup>, which represents a greater therapeutic burden but nevertheless presents more exacerbations<sup>66</sup>. All these characteristics could jointly form a special clinical phenotype of asthma patients. Table 5 shows the characteristics of asthma patients that are currently known to be associated with the appearance of bronchiectasis. It must be stressed that, although bronchiectasis is associated with forms of asthma with greater airway obstruction, this does not mean that bronchiectasis is necessarily associated with airway obstruction, and so the latter is not a pre-condition for its diagnosis.

## Future challenges

It is clear that the information available in the literature at the moment is very scanty and only covers transversal studies aimed at establishing the prevalence of bronchiectasis or some of these patients' characteristics. Longitudinal studies are therefore required to find stronger links between the two diseases and possible shared pathophysiological mechanisms, and, above all, to assess the impact of bronchiectasis on asthma patients, as this probably has prognostic and therapeutic implications. Many questions remain unanswered: What is the real prevalence of bronchiectasis in asthma patients? What is the role of bronchiectasis in the asthma-COPD overlap syndrome (ACOS)? Does the severity or management of asthma affect the presence of bronchiectasis? Could the eosinophil play a role in the genesis of bronchiectasis? Is this an association or is there a causal relationship? In which asthma patients should the presence of bronchiectasis be ruled out? And in which asthma

**TABLE 5.** Characteristics of asthma patients with greater probability of presenting bronchiectasis

Smoker or ex-smoker
More neutrophils in the sputum
Longer duration of the disease
Older age
Poorer pulmonary function
Greater number of exacerbations
Greater need for steroids and bronchodilators
Non-allergic asthma
Greater degree of radiological emphysema
Asthma clinically described as severe (the more severe it is, the greater the presence of bronchiectasis)

patients should the presence of bronchiectasis be ruled out? The current use of low-radiation algorithms for HRCT without any loss of diagnostic capacity provides an extraordinary opportunity to delve further into a topic of great scientific interest and clear practical implications.

## CONFLICT OF INTEREST

The authors have nothing to disclose.

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