Bronchiectasis in COPD patients: more than a comorbidity?

Abstract: Computed tomography scan images have been used to identify different radiological COPD phenotypes based on the presence and severity of emphysema, bronchial wall thickening, and bronchiectasis. Bronchiectasis is defined as an abnormal dilation of the bronchi, usually as a result of chronic airway inflammation and/or infection. The prevalence of bronchiectasis in patients with COPD is high, especially in advanced stages. The identification of bronchiectasis in COPD has been defined as a different clinical COPD phenotype with greater symptomatic severity, more frequent chronic bronchial infection and exacerbations, and poor prognosis. A causal association has not yet been proven, but it is biologically plausible that COPD, and particularly the infective and exacerbator COPD phenotypes, could be the cause of bronchiectasis without any other known etiology, beyond any mere association or comorbidity. The study of the relationship between COPD and bronchiectasis could have important clinical implications, since both diseases have different and complementary therapeutic approaches. Longitudinal studies are needed to investigate the development of bronchiectasis in COPD, and clinical trials with treatments aimed at reducing bacterial loads should be conducted to investigate their impact on the reduction of exacerbations and improvements in the long-term evolution of the disease.

Keywords: COPD, bronchiectasis, infection, exacerbations, natural history, clinical phenotype

Introduction

Patients with COPD may present with different clinical characteristics, prognoses, and response to treatment. This has resulted in increased efforts to identify subgroups of patients that share similar characteristics — the so-called clinical phenotypes — in order to provide more individualized and effective therapy. Some studies have attempted to determine these phenotypes by investigating the morphological findings observed in lung computed tomography (CT) scans. In this respect, the presence of pulmonary emphysema, bronchial wall thickening, and bronchiectasis have been proposed as three of the main morphological findings likely to provide relevant information about different phenotypes of COPD.

Bronchiectasis is defined as irreversible and generally progressive dilation of the airways. Some 30 years ago, Cole proposed a pathogenic vicious circle originating from chronic bronchial infection caused by potentially pathogenic microorganisms (PPMs) and the consequent chronic inflammation which results in remodeling of the airways and damage to local defense mechanisms, which in turn facilitate the persistence of PPMs in the bronchial tree despite the administration of treatment. Chronic bronchial infection is also frequently found in patients with COPD and would provide a link between the two diseases.

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The prevalence of bronchiectasis in patients with COPD has generated several questions. Is there any real increased prevalence of bronchiectasis in patients with COPD? Does the presence of bronchiectasis have an impact on the clinical characteristics, prognosis, or response to treatment in COPD? And, finally, what is the role of chronic bronchial infection and exacerbations in this relationship?

In this respect, O'Brien et al have COPD and bronchiectasis; shouldn't COPD be seen merely as a comorbidity, or as a consequence of the disease's natural history? Is there a causal relationship between COPD and bronchiectasis? If this is the case, what are the pathophysiological mechanisms responsible for this relationship? And, finally, what is the role of chronic bronchial infection and exacerbations in this relationship?

### Table 1

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<td>No relationship with FEV, BODE index, PA isolation or 6MWT</td>
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<td>Agusti et al</td>
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<td>2,164 Prospective 3 years follow-up</td>
<td>63.4 (7.1) 65% males</td>
<td>Characterization of COPD heterogeneity</td>
<td>Consecutive low-dose CT scan GOLD II: 44.1% GOLD III: 42.1% GOLD IV: 13.7% FEV&lt;sub&gt;1&lt;/sub&gt;: 48.3%</td>
<td>No criteria available</td>
<td>4% Stage II: 1%–2% Stage III: 3%–6% Stage IV: 7%–9%</td>
<td>CT scan performed to analyze emphysema quantification</td>
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<td>Bafadhel et al</td>
<td>Stable COPD (only if previous CT scan)</td>
<td>75 Cross-sectional</td>
<td>67 (43–88) 58% males</td>
<td>CT scan COPD phenotypes Non-consecutive HRCT GOLD FEV&lt;sub&gt;1&lt;/sub&gt;: 46%</td>
<td>Naidich (diagnosis) and 0–4 points (grading) Naidich 27%</td>
<td>– No relationship with lung function, exacerbations or bacterial load</td>
<td>– Risk factors for BCH were severe COPD, PPM isolates, and at least one hospital admission in the previous year</td>
<td>– Severe exacerbations – Time to recovery – Decreased FEV&lt;sub&gt;1&lt;/sub&gt; – Bacterial colonization</td>
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<tr>
<td>Martinez-Garcia et al</td>
<td>Stable moderate-to-severe COPD Previous BCH was excluded</td>
<td>92 Prospective 3 years follow-up</td>
<td>71.3 (9.3) 99% males</td>
<td>Factors associated with BCH Consecutive HRCT GOLD Moderate: 44.6% Severe: 55.4%</td>
<td>Naidich More than one segment 57.6%</td>
<td>– Increased exacerbations – Decreased FEV&lt;sub&gt;1&lt;/sub&gt; – Bacterial colonization</td>
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<tr>
<td>Arram and Elrakhawy</td>
<td>Moderate-to-severe stable COPD</td>
<td>69 Cross-sectional</td>
<td>59.4–60.4 95% males</td>
<td>Incidence of BCH Consecutive HRCT GOLD FEV&lt;sub&gt;1&lt;/sub&gt;: 56% Moderate FEV&lt;sub&gt;1&lt;/sub&gt;: 45% Severe</td>
<td>No criteria available</td>
<td>47.8% Moderate 31.3% Severe 62.2% 82% cylindrical 67% lower lobes 73% bilateral</td>
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<tr>
<td>Steward et al</td>
<td>Stable COPD GOLD II–IV COPD Gene</td>
<td>3,752 Prospective</td>
<td>62.8–65.5 55% males</td>
<td>Prevalence and clinical impact of BCH Consecutive CT GOLD</td>
<td>Visual assessment 20.8% GOLD II: 18.8% GOLD III: 24% GOLD IV: 24%</td>
<td>– Increased age, exacerbations, BODE and GOLD stage – Decreased FEV&lt;sub&gt;1&lt;/sub&gt; and BMI – Increased mortality, exacerbations, bacterial isolation including PA and CRP levels</td>
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<tr>
<td>Martinez-Garcia et al</td>
<td>Stable moderate-to-severe COPD. Previous BCH was excluded</td>
<td>201 Prospective 48 months follow-up</td>
<td>70.3 (8.9) 90.5% males</td>
<td>Prognostic value of BCH Consecutive HRCT GOLD GOLD II: 49.2% GOLD III: 42.3% GOLD IV: 8.5% FEV&lt;sub&gt;1&lt;/sub&gt;: 49%</td>
<td>Naidich More than one segment 57.2% 87% cylindrical 81% lower lobes 83 Bhalla score</td>
<td>– Increased exacerbations – Decreased FEV&lt;sub&gt;1&lt;/sub&gt;, and BMI – Increased mortality, exacerbations, bacterial isolation including PA and CRP levels</td>
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<tr>
<td>Tulek et al</td>
<td>Stable COPD (BCH or clinical evidence of BCH was excluded)</td>
<td>80 Cross-sectional</td>
<td>68 (8) 95% males</td>
<td>Radiological COPD phenotypes Consecutive HRCT GOLD FEV&lt;sub&gt;1&lt;/sub&gt;: 57.1% Moderate: 46% Severe: 30%</td>
<td>Naidich Modified Bhalla (grading) 33.8% – 40% in moderate-to-severe patients</td>
<td>– Increased exacerbations, Bhalla score, CRP and ESR concentrations – Decreased FEV&lt;sub&gt;1&lt;/sub&gt; – BCH (score &gt;5) was a risk factor for PA isolation – Mortality was higher in the PA group – CC by mucoid PA was associated with BCH (score &gt;5)</td>
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<td>Gallego et al</td>
<td>Exacerbation of COPD with exacerbator phenotype</td>
<td>118 Prospective 1,003 (306) days follow-up</td>
<td>69.5 (8.2) Predominantly males</td>
<td>Prevalence and risk factors for PA Consecutive HRCT GOLD FEV&lt;sub&gt;1&lt;/sub&gt;: 34% GOLD IV: 60%</td>
<td>Naidich (diagnosis) and Smith (grading) Score ≤1 was considered normal 47% – 52% only in lower lobes – 25% in more than 4 lobes – BCH score: 4.2</td>
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<th>BCH prevalence</th>
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<tbody>
<tr>
<td>Gatheral et al (2014)</td>
<td>First hospitalized COPD</td>
<td>406</td>
<td>Retrospective</td>
<td>71 (11) 56% males</td>
<td>Impact of BCH on clinical outcomes</td>
<td>Non-consecutive HRCT (406/2,414). Not all HRCT (41%).</td>
<td>ICD-10 code: J440/1/8/9</td>
<td>Naidich 0 (absent) –4 severe BCH points (no reference)</td>
<td>69%</td>
<td>Minor (40%) Mild (29%) Moderate (22%) Severe (8%) Increase with age and male gender</td>
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<td>Jairam et al (2015)</td>
<td>COPD without previous exacerbations and CT performed because of non-pulmonary causes</td>
<td>338</td>
<td>Prospective 4.4 years follow-up</td>
<td>71 (61–76) 54% males</td>
<td>Incidental CT findings and risk of hospitalization or death due to COPD exacerbation</td>
<td>Non-consecutive CT</td>
<td>GOLD</td>
<td>Reischner Society Criteria (diagnosis) Score = 1: 14% Score = 2: 9% Score &gt; 2: 9%</td>
<td>32.5%</td>
<td>– No relationship with future exacerbations or death</td>
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<td>Mao et al (2015)</td>
<td>Stable COPD (only if previous CT scan)</td>
<td>896</td>
<td>Retrospective 21 months follow-up</td>
<td>66.2 (9.6) 85% males</td>
<td>Prognostic value of BCH</td>
<td>Non-consecutive HRCT</td>
<td>GOLD</td>
<td>Naidich</td>
<td>34.7%</td>
<td>– PA colonization – Increased all-cause mortality</td>
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<td>da Silva et al (2016)</td>
<td>Stable COPD (previous BCH was excluded)</td>
<td>65</td>
<td>Retrospective 2.5 years follow-up</td>
<td>64.2 (8.5) 66% males</td>
<td>COPD phenotypes on HRCT</td>
<td>Consecutive HRCT</td>
<td>GOLD</td>
<td>Bhalla system</td>
<td>33.8%</td>
<td>– No relationship with functional variables</td>
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<td>Tan et al (2016)</td>
<td>Stable COPD (Canadian cohort)</td>
<td>451</td>
<td>Prospective</td>
<td>62.8–69 46%–50% males</td>
<td>CT abnormalities</td>
<td>Non-consecutive HRCT</td>
<td>Spirometric values (LLN)</td>
<td>Reischner Society Criteria Mild: 14.1% Moderate: 22.2% Severe: 35.1%</td>
<td>– BCH related to higher dyspnea, chronic cough, and wheeze – CAT score ≥10 No relationship with exacerbation frequency</td>
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Characteristics of patients with COPD and bronchiectasis compared with COPD patients without bronchiectasis

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<th>General characteristics</th>
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<td>Older patients</td>
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<td>Higher frequency of males</td>
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<td>Heavier smokers</td>
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<th>Clinical features</th>
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<td>Increased daily sputum production</td>
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<td>Increased number of exacerbations</td>
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<th>Lung function parameters</th>
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<td>More severe airflow obstruction (measured by FEV1/FVC and FEV1 % predicted)</td>
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<th>Inflammatory markers</th>
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<td>Higher levels of peripheral CRP</td>
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<td>Lower concentration of albumin</td>
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<th>Microbiological profile</th>
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<td>Increased prevalence of PPM colonization</td>
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<tr>
<td>Increased prevalence of <em>Pseudomonas aeruginosa</em> colonization</td>
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<th>Prognostic features</th>
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<tr>
<td>Doubled risk of all-cause mortality</td>
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Notes: Based on two meta-analyses by Ni et al11 and Du et al.32 Variables in bold are those with the highest odds ratios in the meta-analysis.

Abbreviations: CRP, C-reactive protein; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity; PPM, potentially pathogenic microorganism.

Moreover, most of these studies excluded patients with previously known bronchiectasis and those with bronchiectasis in only one pulmonary segment, as this circumstance can be found in a significant percentage of elderly people in the general population, or in smokers with no airway obstruction.29 Recently, Tan et al10 found that 19.9% of healthy individuals had bronchiectasis compared with 35.1% of severe COPD patients of the same age. This means that the real prevalence of bronchiectasis in COPD patients might be overestimated, and other CT characteristics such as bronchial wall thickening should be used to differentiate real bronchiectasis in COPD from bronchiectasis associated with aging.13

In patients with COPD the characteristics found to be associated with a higher prevalence of bronchiectasis include advanced age,22 male gender,25 and a history of previous exacerbations.13,15,18,19,23 The bronchiectasis observed in patients with COPD is usually cylindrical (72%–90%), predominantly in both pulmonary bases (52%–81%), bilateral (52%–67%), and with moderate scores in radiological analyses of severity.13–17,21,23 Interestingly, one consistent finding is the relationship between the increased severity of COPD and the higher prevalence of bronchiectasis.16,20,22,24,25

Impact of bronchiectasis on COPD

The impact of bronchiectasis on the natural history of COPD has been analyzed in two recent meta-analyses31,32 and can be summarized as follows (Table 2).

Clinical aspects

The presence of bronchiectasis in COPD has been associated with a lower body mass index,22 older age,22,25 a greater production and purulence of sputum,17 a greater number of comorbidities,25 and a higher body mass index, airflow obstruction, dyspnea, and exercise index.22 However, the most widely recognized association is a greater frequency and severity of exacerbations, identified for the first time by Patel et al,17 and confirmed in subsequent studies.16,22,26

Microbiological aspects

The variable most consistently associated with the presence of bronchiectasis in patients with COPD is chronic bronchial infection by PPMs (odds ratio [OR] between 3.76–7.33), particularly *Pseudomonas aeruginosa* (OR between 3.5–4.75),31,32 along with the existence of a greater bacterial load.17

Functional aspects

There is also significant agreement that the presence of bronchiectasis is associated with more severe bronchial obstruction.13,15,21–23

Inflammatory aspects

The presence of bronchiectasis has been associated with an increase in both local and systemic inflammation.17,22,24 Patel et al17 observed that patients with bronchiectasis presented an increase in the concentrations of IL-8 and IL-6 in sputum as a result of the greater bacterial load. Similarly, two studies observed an increase in C-reactive protein and erythrocyte sedimentation rate in peripheral blood.23,24

Prognostic aspects

Only a few studies have analyzed the relationship between the presence of bronchiectasis and poor outcomes in patients with COPD. A prospective study on 201 consecutive patients with stable COPD followed-up for 48 months concluded that the presence of bronchiectasis was associated with greater mortality (OR: 2.45; P=0.02), independent of age, the presence of comorbidities, or the severity of airway obstruction;21 these results were confirmed by Mao et al.27 In contrast, another two studies — one performed on 406 COPD patients during a severe exacerbation23 and another on 338 patients with no previous exacerbations26 — did not find any association between the presence of bronchiectasis and greater mortality. However, the meta-analysis by Du et al32 concluded that the mortality risk in COPD is significantly increased in the presence of bronchiectasis with an OR of 1.96 (95% confidence interval =1.04–3.70).
Searching for causality: is this possible?
A further advance in our understanding of the interaction between COPD and bronchiectasis would be to know whether bronchiectasis in COPD patients develops as a result of COPD or its determining factors, such as smoking, presence of chronic bronchial infection, and exacerbations.

Even though some etiological classifications of bronchiectasis include COPD as one of its causes, so far no longitudinal study has demonstrated any causal relationship, although Bradford Hill’s classic etiologic criteria could provide the basis for an argument in favor of this possibility.

Strength of association
Two recent meta-analyses concluded that the presence of PPMs (OR: 7.33 and 3.76, respectively), colonization by *P. aeruginosa* (OR: 3.50 and 4.75, respectively), and a greater number of exacerbations (OR: 1.97 and 1.54, respectively) were the variables most strongly associated with the presence of bronchiectasis in COPD. Although it is still unknown whether chronic bronchial infection and frequent exacerbations occur before or after the development of bronchiectasis in patients with COPD, the results of these meta-analyses support the pathophysiological hypothesis that development of bronchiectasis in COPD is associated with chronic bronchial infection and frequent exacerbations.

Time sequence
This would be based on the observation of “de novo” bronchiectasis in COPD patients in whom it was not previously present. Figure 1 shows a patient who, in 2007, presented with severe COPD (forced expiratory volume in 1 second [FEV₁]: 49% predicted), chronic bronchitis, and frequent exacerbations but had no bronchiectasis detected by high-resolution computed tomography (HRCT) scan at that time. The same patient participated in a new study 8 years later, when his FEV₁ was 29% predicted, revealing bibasal cylindrical bronchiectasis. In spite of an exhaustive etiological study, it was impossible to identify any cause for bronchiectasis other than COPD itself. Longitudinal studies involving repeated HRCT are required to confirm a time sequence that would support a causal relationship between the two diseases.

Dose-response effect
The dose-response effect could be applied to the higher prevalence of bronchiectasis observed in patients with a greater severity of COPD.

Consistency
Consistency refers to the percentage of studies that reach the same conclusions. In this respect, most studies have observed not only a high prevalence of bronchiectasis, but also a similar pattern, comprising cylindrical, bilateral, and bibasal bronchiectasis. Furthermore, bronchiectasis seems to be found more frequently in older patients and heavier smokers, which would concur with the hypothesis that bronchiectasis occurs as a consequence of years of bronchial inflammation or infection.

Biological plausibility
Subjects with COPD present different forms of impaired immunity that facilitate the survival and proliferation of

Figure 1 Development of bronchiectasis in a patient with severe COPD.
Notes: (A) HRCT scan without bronchiectasis in 2007 and (B) HRCT scan from the same patient and slide in 2015.
Abbreviation: HRCT, high-resolution computed tomography.
PPMs in the lower airways. In fact, microbiological cultures of sputum are positive for PPMs in about 40%–70% of patients with stable COPD. This chronic bronchial infection unleashes a persistent bronchial inflammation and these two together progressively damage the bronchial wall through the release of bacterial and inflammatory proteolytic products, leading to the formation of bronchiectasis, in accordance with the classic postulates of Cole, described previously. The reduced activity of many antimicrobials as a result of the chronic bronchial infection and the difficult diffusion to the bronchial secretions resulting from the presence of bronchiectasis, makes it much more difficult to eradicate the PPMs, and so the process becomes chronic, thereby increasing the frequency and severity of the exacerbations in a patient with COPD. This sequence of events is illustrated in Figure 2.

**Analogy**

This refers to the existence of similar examples that would explain the relationship that needs to be demonstrated. The origin of bronchiectasis in patients with cystic fibrosis could be a valid example in this respect.

**Experimental evidence**

There is no evidence to date of any delay to, or non-appearance of bronchiectasis in patients with COPD as a result of prophylactic treatment for exacerbations or long-term anti-inflammatory or antibiotic treatment, although this would undoubtedly be one of the main objectives of future studies.

**Bronchiectasis-COPD overlap: comorbidity or a distinct clinical phenotype?**

COPD can exist without bronchiectasis and bronchiectasis is often not present alongside chronic airflow obstruction; however, when bronchiectasis of unknown etiology is demonstrated in a patient with COPD it is difficult to accept that it is merely a comorbidity that appeared by chance. Tobacco smoking is the main etiological factor for COPD, and it also impairs lung defense mechanisms and facilitates chronic and acute infection. The role of infection in the cascade of events that accelerate the progression of COPD in smokers, and how it can be a key player in the development of bronchiectasis, has already been addressed. It is therefore reasonable to assume that in some patients the two diseases, COPD and bronchiectasis, may be clinical manifestations of the same process, justifying the overlapping term or clinical phenotype COPD-bronchiectasis. It is interesting to observe that a significant proportion of patients with bronchiectasis included in clinical trials were also smokers with chronic airflow obstruction. This highlights the strong relationship between these two entities, but is it a case of bronchiectasis with airflow obstruction, or COPD with bronchiectasis? Hurst et al highlighted the importance of differentiating between patients with bronchiectasis who present with not fully reversible airflow obstruction and COPD patients presenting the anatomical abnormalities of bronchiectasis. This second case would fulfil the criteria of a phenotype of the COPD disease spectrum.

The diagnosis of the COPD-bronchiectasis phenotype will have clinical implications for more frequent chronic...
bronchial infection, impairment in respiratory symptoms (cough and sputum), more frequent and severe exacerbations, and impaired health-related quality of life. These signs and symptoms are very similar to those of the COPD-infective phenotype and there must be a huge overlap between them. It can be speculated that the COPD-bronchiectasis phenotype may be a sub-phenotype or an evolution of the infective phenotype of COPD (Figure 3), characterized by chronic bronchial infection by PPMs and frequent bacterial exacerbations. Some patients with COPD and infective phenotype may have developed bronchiectasis, but others may be in the initial stages of the disease and would be susceptible to therapeutic strategies aimed at suppressing bacterial growth and avoiding bacterial persistence, in order to prevent the development of bronchiectasis. Unfortunately, no longitudinal studies are yet available to confirm this sequence of events.

The COPD-bronchiectasis phenotype would also overlap with the chronic bronchitis and frequent exacerbator phenotypes (Figure 3). In contrast to the previously mentioned phenotypes, the COPD-bronchiectasis phenotype is stable and can be objectively diagnosed via imaging. Some national guidelines have included the COPD-bronchiectasis phenotype as an important clinical phenotype that need to be considered in the treatment of COPD.44

**Bronchiectasis in COPD: therapeutic consequences**

Although the presence of bronchiectasis in patients with COPD is usually associated with chronic bronchial infection and more frequent exacerbations, mostly of a bacterial etiology, this infective component is not adequately covered by the usual treatment for COPD based on inhaled therapy with bronchodilators, with or without inhaled corticosteroids (ICS). Some recent studies have demonstrated that even patients on triple therapy may suffer from frequent exacerbations.45 One of the reasons would be the lack of appropriate treatment for the infective component of the disease. An HRCT scan of the thorax must be performed in patients with COPD and frequent exacerbations, and when bronchiectasis is identified, they must receive treatment for both COPD and bronchiectasis, in the latter case mainly aimed at controlling chronic and acute infection.

There have not been any trials of therapies for COPD complicated by bronchiectasis. In most pharmacologic clinical trials on COPD the presence of significant bronchiectasis is an exclusion criterion; therefore, no recommendations can be formulated on the basis of solid evidence, although special attention must be paid to anti-inflammatory and antibiotic therapies.

The efficacy of ICS in COPD is controversial, particularly in patients with frequent bacterial exacerbations and/or low concentrations of bronchial or blood eosinophils, as may be the case in patients with associated bronchiectasis. Furthermore, the use of ICS may be associated with an increase in the bronchial bacterial load in patients with COPD and chronic bronchial infection; in fact, ICS are not indicated as maintenance treatment in bronchiectasis, and the last update of the GOLD strategy indicates that in the case of associated bronchiectasis, ICS may not be indicated in patients with bacterial colonization or recurrent lower respiratory tract infections. Therefore, unless patients present with high blood eosinophil levels and/or clinical signs of bronchial hyper-responsiveness, ICS should not be used.

**Figure 3** Relationship between COPD-bronchiectasis overlap phenotype and infective and chronic bronchitis and exacerbator phenotypes. *Abbreviation: BCH, bronchiectasis.*
or only used at the lowest possible dosage. One alternative may be the use of macrolides or roflumilast, which is effective in neutrophilic inflammation and in patients with chronic cough and sputum production, both characteristics of bronchiectasis in COPD.

There have been therapeutic trials on bronchiectasis that include adult smokers with airflow obstruction that is not fully reversible and similar to COPD. From these trials we can speculate that the use of long-term macrolides or inhaled antibiotics could be beneficial in reducing exacerbations in these patients. Other strategies such as physiotherapy must also be considered.

What do we need from future studies on this topic?
To analyze the true prevalence of bronchiectasis in COPD patients, large studies of consecutive stable COPD patients from international registries should be performed. Bronchiectasis diagnosis should be made by means of HRCT scans interpreted with uniform radiological criteria, taking into account the existence of bronchial dilations mimicking bronchiectasis in the elderly.

The causal relationship between COPD and bronchiectasis requires longitudinal studies to be adequately assessed. These studies should include evaluation of the lungs by repeated HRCT scans to verify the development of “de novo” bronchiectasis in subjects with COPD, and they should investigate the related factors that predispose to this association. Longitudinal studies should also confirm the prognostic impact of bronchiectasis on outcomes such as exacerbations, hospitalizations, and mortality in COPD.

Another interesting aspect for future research is the study of specific biomarkers linking COPD and bronchiectasis, especially those related to neutrophilic inflammation, COPD severity, exacerbations, bronchial wall thickening, or increased susceptibility to chronic bronchial infection. The composition and relevance of the lung microbiome and its changes with the evolution of the disease, or with treatment, provide another area for future research.

Finally, therapeutic trials should be conducted on patients with COPD and bronchiectasis to investigate the efficacy and safety of specific treatments such as mucolytics, phosphodiesterase IV inhibitors, long-term macrolides, and inhaled antibiotics, particularly in more severe patients with a high risk of exacerbations and chronic bronchial infection.

Conclusion
The prevalence of bronchiectasis in patients with COPD is high. Some of the etiological factors for bronchiectasis are present in patients with COPD, and may be responsible for the development of bronchiectasis in susceptible individuals. It is not clear why some patients with COPD develop bronchiectasis and others do not, but the presence of a chronic bronchitis phenotype may determine an increased risk of chronic bronchial infection and recurrent infective exacerbations, which perpetuate the vicious circle of infection, inflammation, and tissue destruction. The presence of bronchiectasis in COPD is associated with more frequent and severe exacerbations, impaired quality of life, and possibly reduced survival. Longitudinal studies are needed to investigate the development of bronchiectasis in COPD, and clinical trials with treatments aimed at reducing bacterial loads should be conducted to investigate their impact on the reduction of exacerbations and improvements in the long-term evolution of the disease.

Disclosure
The authors report no conflicts of interest in this work.

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