**Review Article**



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# COPD and Bronchiectasis Overlap: Coincidence or Phenotype?

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The coexistence of chronic obstructive pulmonary disease (COPD) and bronchiectasis is increasingly recognized as a distinct clinical phenotype that presents unique diagnostic and therapeutic challenges. This overlap syndrome is characterized by heightened airway inflammation, frequent bacterial colonization, and a greater burden of respiratory symptoms, leading to poorer clinical outcomes. In this review, we explore the pathophysiological mechanisms underlying COPD-bronchiectasis overlap, emphasizing the role of chronic infection, impaired mucociliary clearance, and structural lung damage in driving disease progression. Bronchiectasis in COPD patients is associated with increased airflow obstruction, higher exacerbation rates, and greater disease severity compared to COPD alone. The shared pathophysiology includes chronic inflammation, often initiated by cigarette smoke or other environmental pollutants, and recurrent infections, especially with pathogens like Pseudomonas aeruginosa. These infections create a vicious cycle of inflammation and bronchial wall damage, resulting in airway dilation and impaired lung function. Diagnosing bronchiectasis in COPD patients remains challenging due to overlapping symptoms. High-resolution computed tomography (HRCT) is essential for identifying bronchial abnormalities, while spirometry confirms obstructive patterns. This review also highlights the need for tailored therapeutic strategies, including aggressive management of infections, use of long-acting bronchodilators, and cautious application of inhaled corticosteroids, which may exacerbate inflammation in patients with bronchiectasis. By recognizing COPD-bronchiectasis overlap as a distinct phenotype, we aim to improve clinical outcomes through a more personalized and comprehensive approach to diagnosis and treatment, ultimately enhancing patient quality of life.

**Keywords:** Bronchiectasis; COPD; Overlap Syndrome; Phenotype

## INTRODUCTION

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, and/or exacerbations) due to abnormalities of the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction, associated with pollutant exposures (1). The estimated prevalence of COPD is about 13.1% and ranks as the third leading cause of death worldwide (2).

COPD is considered a multifactorial disease with cigarette smoke being the most important risk factor, as we do not exclude the fact that non-smokers can also develop the disease (1,2). According to estimates, 25-45% of cases of COPD are non-smokers who have been exposed either to

environmental factors (including air pollution from biomass smoke, occupational exposure to dust, benzene and chemical gases in the workplace), or due to genetic background with mutations in the SERPINA 1 gene which lead to lack of a1- antitrypsin and is associated with reduced lung function (3). Based on estimates from the Global Burden of Disease (GBD) study, 251 million cases of COPD were recorded in 2016 (3). This obstructive disease is a real challenge for global health systems with significant socio-economic and health consequences due to high costs and negative impacts on patients' quality of life (3).

The gold standard for the diagnosis of COPD is the spirometry with the most commonly used diagnostic criteria being the ratio (Forced Expiratory Volume in one second/ Forced Vital Capacity, FEV1/FVC<0.7), less than 70% in a patient with a smoking habit of more than 10 packs-years (2), or a ration below the lower limit of normal (LLN) criteria (3).

Bronchiectasis, on the other hand, is defined as the permanent and progressive pathological dilation of the airways because of a vicious circle that destroys the mucosal system and the bronchial wall (2). It is another chronic condition described as one of the most neglected diseases in respiratory medicine (4). Patients experience chronic cough, sputum production, shortness of breath, fatigue, and repeated exacerbations. They have extreme clinical variability and affect every age group due to the great heterogeneity of the disease (4). Bronchiectasis is increasingly recognized as a significant public health issue, with rising prevalence rates globally (4,5). A relatively recent national cohort study in the Chinese urban population showed an increase in bronchiectasis prevalence 2.31 times more than 75.48 cases per 100,000 person-years in 2013 to 174.45 cases per 100,000 person-years in 2017 (6). In general, the prevalence of bronchiectasis seems to be higher in women than in men and increases with age (6,7). However, recent studies have shown a more pronounced increase in prevalence in males over 60 years of age, which is believed to be attributed to the higher proportion of smokers, particularly men with COPD, in this age range (7).

The main criterion for diagnosing the presence of bronchiectasis is the increase in the diameter of the airways in relation to the neighboring vessel >1 (greater than one) and the thickening of the airway wall during imaging, usually in a CT scan, and is a structural diagnosis (2,4,8). The disease is considered clinically significant when there are imaging abnormalities associated with symptoms of persistent or recurrent bronchial infection (9). The management of bronchiectasis has historically been challenging due to the lack of large-scale, high-quality randomized controlled trials (RCTs). As a result, many guidelines have relied on expert opinion and lower-quality evidence (4). However, in recent years, there has been a growing body of research, including RCTs, that has contributed to a more evidence-based approach, especially regarding the use of long-term antibiotics, airway clearance techniques, and inhaled therapies (4,5). However, the complexity and heterogeneity of bronchiectasis as a condition mean that there is still a reliance on expert opinion, particularly in areas where high-quality evidence is lacking.

Bronchiectasis is now increasingly recognized for its frequent coexistence with COPD, particularly in patients with severe disease (10). This overlap is frequently encountered in clinical practice, creating a complex phenotype that presents unique diagnostic and therapeutic challenges (11–13). Despite its clinical relevance, there remains a substantial gap in our understanding of its pathophysiology and optimal management strategies (11–13). Previous reviews, such as those by Polverino et al. (14) and Alam et al. (15), have described the coexistence of bronchiectasis and COPD.

However, the present review provides an updated synthesis integrating recent evidence on microbiome, genetic, and immunologic mechanisms, as well as therapeutic implications. By emphasizing precision-medicine perspectives and emerging biomarkers, our review advances current understanding of BCOS and highlights potential research directions. Within this context, we aimed to underscore the concept of

overlapping COPD and bronchiectasis as a potential new phenotype within COPD, exploring the research gaps in pathophysiology and diagnosis. By recognizing this overlap as a distinct phenotype, we seek to enhance clinical understanding and management of COPD patients, ultimately leading to improved prognostic outcomes and personalized treatment approaches.

## MATERIALS AND METHODS

We conducted a narrative review of the literature by searching PubMed/MEDLINE, Scopus, and Web of Science from January 2010 to November 2024 using combinations of the terms: "bronchiectasis", "COPD", "overlap", "BCOS", "phenotype", "endotype", "treatable traits", "exacerbations", and "microbiome". We prioritized clinical trials, cohort studies, guideline/consensus statements, and high-quality narrative or systematic reviews. Reference lists of key articles were hand-searched to identify additional sources. Articles not in English, single-patient case reports (unless seminal), and non-peer-reviewed items were excluded. As this is a narrative synthesis, formal risk-of-bias scoring was not performed; instead, study design, sample size, and consistency of findings informed the weighting of evidence.

## DISCUSSION

### Pathophysiology of Bronchiectasis in COPD

The most common comorbidities of COPD are coronary artery calcification, emphysema, and bronchiectasis at rates of 79.8%, 62.7%, and 33.9%, respectively, in a recent study (16). Bronchiectasis was first defined as a comorbidity of COPD in 2014 in the Global Initiative for COPD (17).

Often, patients with COPD suffer from persistent symptoms of cough and sputum production, impairment of respiratory function with the onset of shortness of breath, and frequent exacerbations (11,12). The pathophysiology of bronchiectasis in COPD is multifactorial (13,18), involving chronic inflammation, recurrent infections, and impaired mucociliary clearance. Understanding these mechanisms is essential for optimizing the management and treatment of affected patients (2).

COPD is characterized by chronic inflammation of the airways due to long-term exposure to irritants like cigarette smoke (19). This persistent inflammation leads to structural changes in the lungs, such as fibrosis and narrowing of the airways. In COPD patients, the chronic inflammatory state creates an environment conducive to the development of bronchiectasis. The inflammation weakens the bronchial walls and disrupts the normal repair processes, leading to the progressive destruction and dilation of the bronchi (2,20).

The compromised immune mechanisms and frequent lower airway infections in COPD patients contribute to a cycle of chronic bronchial inflammation. When pathogens are not effectively managed, this inflammation, driven by bacterial and inflammatory proteolytic products, leads to the destruction and structural alteration of the bronchial walls, which can result in bronchiectasis (18-21). Structural changes in the lungs due to COPD, such as airway remodeling and emphysema, further exacerbate this process by increasing airway pressure during exhalation, causing additional bronchial dilation (2,18-22). Emphysema, characterized by the destruction of alveolar walls and loss of lung elasticity, leads to increased airway pressure during exhalation, causing further dilation of the bronchi (18-22).

A critical factor in the development of bronchiectasis in COPD is the impairment of mucociliary clearance, which is caused by the destruction of ciliated epithelial cells and excessive mucus production. This impairment leads to mucus accumulation, creating an environment conducive to chronic bacterial colonization, particularly by pathogens such as Pseudomonas aeruginosa (2,17-21). This colonization drives a vicious cycle of infection and inflammation, further damaging the airways, thickening bronchial walls, and increasing airway resistance, all of which contribute to the progression of bronchiectasis (17-21).

Furthermore, the presence of pathogens like *Pseudomonas aeruginosa* in the airways is associated with more severe COPD, frequent exacerbations, and accelerated decline in lung function. The immune response to these pathogens releases proteolytic enzymes and inflammatory mediators, which degrade the bronchial walls, making them more susceptible to ongoing infection and structural damage, thus reinforcing the development and progression of bronchiectasis in COPD patients (13,18).

### Bronchiectasis Can Lead to Airway Obstruction

Bronchiectasis, characterized by the permanent dilation of the bronchi, leads to significant structural changes within the airways that contribute to the development of airway obstruction. The pathophysiological mechanisms underlying this progression are complex and multifactorial, involving chronic infection, inflammation, and remodeling of the airway walls (2,17).

The core of bronchiectasis pathophysiology is a vicious cycle of chronic infection and inflammation, as described by Cole's "vicious cycle hypothesis". In this model, chronic bacterial infections, particularly with pathogens such as Pseudomonas aeruginosa, drive persistent inflammation within the bronchi. This inflammation leads to the release of proteolytic enzymes, cytokines, and other inflammatory mediators, which damage the bronchial wall, degrade the extracellular matrix, and destroy the ciliary structure, impairing mucociliary clearance (18,19). Due to the complexity of Cole's formulation, there is a suspicion that genetic background and genome, as well as a variety of environmental factors, can play a huge and decisive role in the onset and progression of bronchiectasis (11)

The damage to the cilia and the increased mucus production result in impaired mucociliary clearance. Mucus accumulation within the dilated bronchi provides a breeding ground for bacteria, perpetuating the cycle of infection and inflammation. The inability to clear mucus effectively not only promotes chronic infection but also contributes directly to airway obstruction as the mucus plugs block the airways, increasing resistance to airflow (2,18,20).

The chronic inflammatory state in bronchiectasis leads to structural changes in the airways, including bronchial wall thickening, fibrosis, and loss of elasticity. These changes result in the narrowing of the airways, which further obstructs airflow (14,21). Additionally, the dilated bronchi can compress adjacent smaller airways, leading to increased resistance to airflow during expiration, a hallmark feature of obstructive lung diseases (2,17). Over time, the continuous cycle of inflammation and repair leads to significant remodeling of the airway structure. This remodeling includes thickening of the airway walls, fibrosis, and smooth muscle hypertrophy, which contribute to the progressive nature of airway obstruction in bronchiectasis (17). The increased airway resistance and decreased airflow are characteristic features of obstructive lung disease, which are often seen in patients with bronchiectasis, particularly when it coexists with COPD (21).

### COPD-Bronchiectasis overlap

COPD and bronchiectasis frequently coexist, creating a clinical scenario known as the COPD-bronchiectasis overlap. Consequently, people with overlap have significant damage to the defense mechanisms of the lungs, which leads to an abundance of prolonged inflammation and colonization by potentially pathogenic microbes (PPMs) (13-17). Many times, we observe patients in whom COPD and bronchiectasis overlap without knowing exactly what precedes it (22). The overlap of COPD and bronchiectasis was first formally described by Barker in 2002 (23). Many studies suggest that in patients with moderate or severe COPD, the prevalence of bronchiectasis is constantly increasing, resulting in a worse clinical picture associated with intense inflammation of the bronchi (2).

Studies have since shown that the prevalence of bronchiectasis increases with the severity of COPD, ranging between 20% and 60% in moderate to severe cases (13). The COPD-bronchiectasis overlap represents a significant clinical challenge due to the compounded effects of both conditions on the respiratory system. While

the relationship between these two conditions has been observed in clinical practice, studies like the EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) study have provided deeper insights into the prevalence, clinical characteristics, and outcomes associated with this overlap (17,21). The EMBARC study has highlighted the high prevalence of bronchiectasis among patients with moderate to severe COPD. According to EMBARC findings, bronchiectasis is present in up to 50% of COPD patients with moderate to severe disease, underscoring the need for careful diagnostic assessment in this population (4,17).

Unfortunately, until today, it has not been established whether this relationship between the two respiratory diseases is causal or is a simple random correlation (20). However, there is a prevailing theory that several infectious and aggravating phenotypes of COPD could be a cause (17). The CanCold study investigates whether tobacco smoke is an important factor in the development of bronchiectasis compared to healthy adults, smokers without respiratory problems, and patients with COPD. It found that the prevalence of bronchiectasis in both healthy subjects and smokers without COPD is the same, 19.9% (21). Many studies indicate that colonization by pathogenic microorganisms, particularly *Pseudomonas aeruginosa*, is a primary risk factor associated with the pathophysiological mechanisms leading to the development of bronchiectasis in COPD patients (13).

The presence of bronchiectasis in COPD patients is associated with a worse clinical picture, including heightened bronchial inflammation, impaired lung function, and a higher frequency of exacerbations, increased bacterial colonization, and a greater burden of symptoms. (2). This overlap significantly impacts patient outcomes, including higher hospitalization rates, higher mortality rates, and reduced quality of life (24). The EMBARC study has also shown that patients with COPD and coexisting bronchiectasis have worse clinical outcomes compared to those with COPD alone (4). Another study identified COPD as the leading cause of non-postinfectious bronchiectasis, accounting for 33% of cases (19). The study also found that patients with both COPD and bronchiectasis had a 43% increased risk of future exacerbations, a doubled mortality risk, and significantly reduced quality of life (19). These findings underscore the importance of recognizing and managing the overlap to implement appropriate therapeutic strategies that can improve patient outcomes and reduce the burden on healthcare systems (21).

However, the sequence of events leading to the coexistence of these two conditions remains unclear, and the relationship between them—whether causal or coincidental—has not been definitively established (21,23). The pathophysiology of the COPD-bronchiectasis overlap involves multiple mechanisms, primarily driven by chronic infection and inflammation. In COPD, the inflammation of the small airways and alveolar destruction lead to airflow limitation. When bronchiectasis is present, these effects are compounded by additional factors such as mucus plugging, bronchial wall thickening, and structural airway changes. These factors contribute to a more severe form of airway obstruction, which is a hallmark of the overlap syndrome (17). When bronchiectasis coexists with COPD, the obstructive effects of both conditions are compounded. The airway obstruction in COPD, primarily due to small airways inflammation and alveolar destruction, is exacerbated by the additional airway blockage caused by mucus plugging and bronchial wall thickening in bronchiectasis (17).

Diagnosing bronchiectasis in the context of COPD can be challenging due to the overlapping symptoms. HRCT is the gold standard for diagnosing bronchiectasis, as it reveals the characteristic bronchial dilation and wall thickening (9,10). However, the diagnosis of COPD is typically based on spirometry evidence of obstructive physiology, highlighting the need for careful evaluation to identify both conditions accurately (2).

The findings from the EMBARC study suggest that HRCT should be considered in COPD patients who present with frequent exacerbations, chronic sputum

production, and bacterial colonization to diagnose bronchiectasis. The study underscores the importance of targeted antibiotic therapy, aggressive management of exacerbations, and comprehensive care strategies that address both COPD and bronchiectasis to improve outcomes. Additionally, the EMBARC study highlights the potential role of biomarkers and new imaging techniques in identifying patients at risk for this overlap syndrome (17,18).

Although COPD is often cited as a causative agent of bronchiectasis, so far, there are no longitudinal studies that have proven a causal relationship (2). COPD and bronchiectasis share common symptoms, including chronic cough, repeated hemoptysis accompanied by sputum, and the development of a hypersensitive lower respiratory tract (19). Clinicians measure serum immunoglobulins to evaluate bronchiectasis, although they are not included in the guidelines for patients with COPD (20).

The studies by Ni et al. and Du et al. report odds ratios (ORs) for three key variables: PPMS (presumably referring to a specific marker or syndrome), exacerbations, and colonization by *Pseudomonas aeruginosa* (17,22).

Ni et al. found that the presence of PPMS had an OR of 7.33, indicating a strong association with bronchiectasis (17). They also reported ORs of 1.97 for exacerbations and 3.50 for *Pseudomonas aeruginosa* colonization, suggesting these are significant, though less strongly associated factors (17). Similarly, Du et al. identified an OR of 3.76 for PPMS, 1.54 for exacerbations, and a higher OR of 4.75 for *Pseudomonas aeruginosa* colonization, emphasizing the critical role of this pathogen in the development of bronchiectasis among COPD patients (22). These findings collectively underscore the importance of these variables, particularly *Pseudomonas aeruginosa* colonization, in the pathogenesis of bronchiectasis in COPD patients.

## Why are there difficulties in correctly diagnosing this overlap?

Although the burden of Bronchiectasis-COPD overlap is now recognized, diagnostic delays remain. Although the two diseases are associated with inflammatory pathways and have common risk factors, the diagnosis of COPD is based on obstructive physiology (25), while bronchiectasis is based on bronchial morphology as shown by HRCT scan (26), which can lead to similar abnormalities of the pulmonary parenchyma and difficulties in respiratory function (17). When clinicians encounter patients with smoking habits and the characteristic symptomatology: respiratory distress and coughing with sputum, the first possible scenario they think of is COPD using the spirometer. Thus, we conclude that COPD is widely diagnosed and even wrongly diagnosed, as health professionals should suspect the presence of bronchiectasis using a chest CT scan (26). One third of patients referred from primary health care with a diagnosis of COPD had bronchiectasis even with normal spirometric values (10).

The bronchiectasis that occurs in these patients is mainly cylindrical and is located at the bases of the lungs bilaterally, as radiological findings have shown. Additional common findings of the two diseases are neutrophilic inflammation as well as neutrophilic elastase in patients' sputum, mucus, and bacterial load, with an increase in IL-8 concentrations of IL-6, C-reactive protein, and erythrocyte sedimentation rate in peripheral blood (17), signaling an immune imbalance (18).

## Microbiome and genetic targets

The microbiota and heterogeneity of the airway microbiome play an important role in the development and progression of disease, affecting both the pathology and the effectiveness of the recommended therapeutic approach (27). Research has shown that the microbiome that dominates Pseudomonas in patients with bronchiectasis has an increased risk of exacerbations and worsening of disease symptoms (12). This results in poor clinical outcomes and an increase in several markers such as CRP and neutrophilic elastase due to prolonged neutrophilic inflammation, as shown in several proteomics sputum studies in patients (11). The role of the microbiome in the COPD-bronchiectasis overlap has not been sufficiently studied. However, the use of metagenomics with the sequencing of all extracted DNA may succeed in revealing its composition and diversity (12).

Despite the pathophysiological model developed by Cole, there are huge gaps in understanding the development of bronchiectasis. Knowledge of the genetic background in relation to environmental factors that can modify gene expression, and the use of genetics, epigenetics, transcriptomics, and proteomics, can be a huge step towards having personalized treatment for the profile of each patient according to precision medicine. By studying heredity, the identification of single-nucleotide polymorphisms (SNPs), the analysis of the entire human genome, and understanding the importance of epigenetics, we can gain a better insight into the development of bronchiectasis and the overlap between these two entities (11).

## Therapeutic approach

According to current guidelines, patients with overlapping COPD-bronchiectasis should be treated for the two conditions simultaneously (19). However, there have not been the required clinical trials for these patients, as the study of treatments in patients with COPD excludes the possibility of the coexistence of bronchiectasis (17).

Nowadays, clinicians use long-acting bronchodilators (LAMAs) and beta-2 long-acting agonists (LABAs) (28) to treat chronic obstructive pulmonary disease, which improves airflow restriction and relieves the patient from the unpleasant symptoms of the disease. PPE-4 inhibitors also work as an anti-inflammatory therapy in patients with COPD who have a high risk of severe exacerbations (29). Inhaled corticosteroids (ICS) are an important class of drugs with anti-inflammatory and immunosuppressive capacity and are widely used in respiratory diseases such as asthma and in cases of eosinophilic inflammation (31). However, the use of ICS in a disease dominated by neutrophilic inflammation can exacerbate it by delaying neutrophil apoptosis and making the body susceptible to the growth of streptococcus-dominant pathogenic bacteria by suppressing cathelicidin antimicrobial peptides (LL-37) (30). Therefore, inhaled corticosteroids (ICS) are not indicated for the treatment of bronchiectasis. Furthermore, according to the GOLD 2024 update, ICS should also be avoided in patients with chronic bacterial colonization and recurrent lower respiratory tract infections because they may increase the bacterial burden (17,31).

An alternative and effective solution for patients with neutrophilic inflammation is the use of roflumilast macrolides, which in therapeutic trials in smokers with bronchiectasis showed a reduction in exacerbations (17). Macrolide antibiotics are a class of drugs with antibacterial and immunomodulatory properties that appear to have a positive effect on respiratory diseases such as asthma, COPD, bronchiectasis due to Pseudomonas colonization, and cystic fibrosis (30). Donath and colleagues showed that macrolides can significantly reduce the risk of COPD exacerbation with the following epidemiological data: RR reduction 37%, RR 0.63, 95% CI 0.45–0.87, p=0.005. However, healthcare professionals should be cautious as there are no randomized clinical trials to accurately confirm the scientists' claims (32).

In conclusion, raising citizens' awareness about smoking cessation through information campaigns and adopting health behaviors for a better quality of life, educating patients suffering from this condition for regular monitoring over time with chest CT scan, as well as vaccination against pneumococcus and influenza, can be important steps for the immediate prognosis and rehabilitation of these patients (9).

## Future directions

It is widely known that there are huge research gaps and pending issues regarding patients with the overlap of the two entities. To collect enough epidemiological data on patients suffering from COPD who develop bronchiectasis in the lower lobes of the lungs, such as prevalence and morbidity, mortality, and the number and severity of exacerbations. Long-term, multinational, and longitudinal studies with international cohorts should be conducted to reduce the risk of systematic error (bias) in selecting participants and collecting information, leading future studies with greater validity and accuracy (17,21).

The study of the microbiome of the lower respiratory tract (27), the attempt to detect endotypes with common

pathophysiological pathways associated with genetic variants and the use of epigenetics and proteomics (11) can contribute positively to the detection of biomarkers associated with the two diseases, with characteristic findings of neutrophilic inflammation and the reduction of the body's defenses against potential pathogens leading to chronic bronchial infection.

In addition, the determination of bronchiectasis should be performed through a variety of criteria in addition to the correlation of the diameter of the adjacent vessel, investigating various qualitative characteristics of patients and anthropometric variables, using HRCT with characteristic radiological findings, i.e., the dilation and thickening of the bronchi walls.

Finally, clinical trials should be conducted on inhaled antibiotics, mucolytic drugs, phosphodiesterase IV inhibitors (PDE-IV), and mainly on long-term use of macrolide antibiotics to detect the effectiveness of treatments in patients with the overlap of COPD and bronchiectasis and personalization of the treatment approach (17).

## CONCLUSION

In conclusion, it is worth noting the high prevalence of bronchiectasis in patients with COPD, which is associated with a worse clinical picture and prognosis, with chronic recurrent inflammation and colonization of microbes in the bronchial tree, an increase in the number and severity of exacerbations, decrease in patients' quality of life, and increase in mortality and revolutionize their introduction into health structures. There are several pathophysiological gaps in the development of this overlap, as we do not know what precedes it, and we cannot answer precisely why some patients with COPD have extensions and some do not. Finally, of great clinical importance will be the conduct of long-term clinical studies to investigate effective treatments to reduce bacterial load and relieve patients from the symptomatology of the disease.

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