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Early View

Review

The overlap between bronchiectasis and chronic airways diseases: state of the art and future directions

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TITLE: The overlap between bronchiectasis and chronic airways diseases: state of the art and future directions

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Abstract

Bronchiectasis is a clinical and radiological diagnosis associated with cough, sputum production and recurrent respiratory infections. The clinical presentation inevitably overlaps with other respiratory disorders such as asthma and COPD. In addition, 4% to 72% of patients with severe COPD are found to have radiological bronchiectasis on CT scanning, with similar frequencies (20-30%) now being reported in cohorts with severe or uncontrolled asthma. Co-diagnosis of bronchiectasis with another airways disease has been reported to be associated with increased lung inflammation, frequent exacerbations, worse lung function and higher mortality. In addition, many patients with all three disorders suffer from chronic rhinosinusitis and upper airway disease resulting in a complex “mixed airway” phenotype.

The management of asthma, bronchiectasis, COPD and upper airway diseases has been traditionally outlined in separate guidelines for each individual disorder. Recognition that the majority of patients have one or more overlapping pathologies requires a re-evaluation of how we treat airway disease. The concept of treatable traits promotes a holistic, pathophysiology based approach to treatment rather than a syndromic approach and may be more appropriate for patients with overlapping features.

Here we review the current clinical definition, diagnosis, management and future directions for the overlap between bronchiectasis and other airway diseases.

Introduction

Due to increasing knowledge and awareness, bronchiectasis are currently considered not a rare condition but a relevant chronic lung disease characterized by permanent bronchial damage and a broad spectrum of chronic respiratory and systemic symptoms[1]. From a radiological perspective, the most accepted criteria were defined by Naidich et al. by a number of direct (Broncho-arterial ratio greater than 1, lack of bronchial tapering, visualization of peripheral bronchi within 1 cm of the costal pleuraIn contact with the mediastinal pleura) and indirect signs(Peribronchial thickening, mucus plugging, mosaic pattern, centrilobular nodules, tree-in-bud nodules, focal areas of air trapping, atelectasis/consolidation)[2][3]. One of the major characteristics of bronchiectasis patients are their heterogeneity. In fact, bronchiectasis patients can present very variable age of presentation (from early life to older age), burden of symptoms (from intermittent dry cough to daily bronchorrhea and frequent exacerbations) and a different prognosis depending on numerous factors such as underlying causes, presence of chronic *Pseudomonas aeruginosa* infection, and comorbidities[1, 4–6].

It is well known that the underlying causes of bronchiectasis can be responsible for relevant differences in terms of clinical presentation, evolution and prognosis. This is particularly evident in case of some pathological conditions such as associated respiratory diseases (chronic obstructive pulmonary disease – COPD-, asthma, allergic bronchopulmonary aspergillosis –ABPA-, sinusitis) or systemic inflammatory diseases (rheumatoid arthritis)[7–12]. Some recent studies suggest that bronchiectasis and COPD co-existing in 20-60% of cases[8]. Furthermore, studies describe increased symptoms' burden, reduced therapeutic arsenal, and worse prognosis compared to COPD or bronchiectasis alone[8, 9, 13, 14]. Unfortunately, it is not completely clear whether the relationship between these two respiratory conditions is a causal connection or a chance association. Nevertheless, the coexistence of bronchiectasis and COPD deserves special attention in terms of therapy and prevention of disease progression.

In most recent years, the description of asthma and bronchiectasis association has shown potentially specific features in terms of age, clinical presentation, risk of

exacerbations, diagnostic and therapeutic options[4, 7, 15]. Unfortunately, there is still limited information on the prognosis of asthma and bronchiectasis overlap, although it has been suggested that severe asthma patients with bronchiectasis may have worse prognosis (more symptoms and exacerbations) than other asthma patients without bronchiectasis[16–18].

In addition, more recently, it has been shown that ABPA and asthma play a considerable role in bronchiectasis[4, 19]. Once again, the nature of this association is not completely understood but the clinical presentation and therapy of ABPA are characteristic and very specific, unlike other bronchiectasis subgroups, suggesting, thus, it is a specific clinical entity more than an overlap between two different conditions.

Up to 75% of bronchiectasis patients may have upper airways disease and present severe daily symptoms of nasal congestion, facial pain, and/or loss of smell[20]. Primary ciliary dyskinesia is a frequent cause of chronic rhino-sinusitis and bronchiectasis, but rhino-sinusitis is relatively frequent in bronchiectasis even in absence of primary ciliary dysfunction[21]. Common predisposing factors or the obvious anatomical connection between upper and lower airways could explain this strong association. Such upper airway symptoms are also common in asthma and COPD.

An important attribute to the mechanism of airway disease is the nature of the bronchial inflammatory process. In bronchiectasis, it has been demonstrated that inflammation is predominated by neutrophils, with elevated levels of IL-8[6, 22–25]. In a study exploring inflammatory cells in sputa of patients with bronchiectasis, neutrophils predominated over eosinophils, with a large variance between patients: median neutrophil percentage was 79% (range, 1.5-98%), and eosinophils- 0.8% (range, 0-70%) [23]. In this cohort, 26% of patients had upper airway involvement, and 16% had airway reversibility. Elevated neutrophils in sputum were associated with more exacerbations, low lung function, and greater duration and severity of bronchiectasis. Similarly, Neutrophil elastase, derived from neutrophils, was found to be associated with an increased severity of bronchiectasis[25]. Inflammatory

mediators in sputa of bronchiectasis were also found to be heterogeneous, with increased levels of IL-8, IL-13, TNFα, and IL17, and elevated levels of IL-4, a type -2 mediator, in a minority of patients. Increased IL-17 predominated in bronchiectasis secondary to primary immune- deficiency, but otherwise no differences were found in groups of patients with different bronchiectasis etiologies[6]. In asthma and CRS, inflammation is heterogeneous, but the majority of patients have an eosinophilic, TH2 mediated inflammation[26]. Similarly, in COPD there is evidence for neutrophil mediated inflammation, but recently, sputum eosinophilia has been suggested to be associated with more exacerbations. In view of the heterogeneity of airway inflammation in bronchiectasis, it may be possible that different inflammatory profiles explain the differences in clinical phenotypes and overlapping airway diseases.

In addition to these chronic inflammatory diseases, gastro-esophageal reflux disease is also considered associated with bronchiectasis, particularly in presence of non-tuberculous mycobacterial (NTM) infection, although its causal relationship has not been demonstrated[27, 28]. The hypothesis is that recurrent GE reflux could irritate upper airways, cause bronchial hyper-responsiveness and also lung infections such as, for instance, aspiration pneumonia or NTM infection, and consequently bronchiectasis. On the other hand it seems that GERD could worsen the symptoms of bronchiectasis and a Korean group suggested that treatment with proton-pump inhibitors in bronchiectasis patients with high body mass index could improve lung function[29]. However the same association between GERD and worsen respiratory symptoms can be invoked for asthma, CRS and COPD[30, 31]. Although the association between GERD and all these airways chronic diseases is clear a causal connection cannot be established nowadays and further investigation considering potential confounding factors is surely needed.

In addition, it is worth reminding that Cystic Fibrosis (CF) is also a cause of bronchiectasis but due to its peculiarities in terms of pathophysiology (genetic defect of the CF transmembrane conductance regulator –CFTR) and clinical management (systemic disease, CFTR modulator therapies) it is not covered in this review [32–34].

Another inheritable but polygenic condition that also causes bronchiectasis is Primary Ciliary Diskynesia (PCD). This is a rare condition whose genetics and pathophysiology are still not fully known. Tipically, PCD patients show sinuses and ears involvement, apart from bronchiectasis, but also a variable combination of fertility disorders and in rare cases “situs inversus”[21, 35].

In the face of the heterogeneity of bronchiectasis, investigation of pathophysiological determinants, clinical outcomes and prognostic factors of specific subgroups or phenotypes can be crucial to improve the management of this disease. An emerging concept in respiratory medicine is the recognition of overlap syndromes which have specific diagnostic, prognostic and therapeutic implications, with asthma COPD-overlap and interstitial pulmonary fibrosis with emphysema being examples of well characterized multipathology syndromes[36–40].

This manuscript will focus on the most common associations between bronchiectasis and other chronic respiratory diseases in order to review current evidence and to outline major research needs.

Overlap COPD and bronchiectasis

Prevalence of bronchiectasis in COPD patients.

There is a lack of large epidemiological studies in patients with COPD employing high-resolution computed tomography (HRCT) to assess the prevalence of bronchiectasis; therefore, there are only few prevalence estimates of this association (table 1). However, despite the possibility of chance coexistence of bronchiectasis and COPD in the same patient and the frequent misdiagnosis of the two conditions[41], the majority of case-series in patients with severe COPD have identified a high frequency of bronchiectasis ranging from 4% to 72%[8, 42]. Several reasons may account for this wide range of prevalence; misdiagnosis is frequent with the presence of vascular hypertension and the performance of CT scans without high-resolution algorithms as the main causes of under-diagnosis of bronchiectasis. In contrast, erroneous diagnosis (over-diagnosis) of bronchiectasis in COPD may be caused by situations such as the

presence of bronchial dilatations present in healthy elderly individuals, interstitial lung diseases or emphysema usually without bronchial wall thickening among others (table 2a). The limitations in the design of studies also account for the mis-diagnosis of bronchiectasis in COPD. The retrospective design of some studies, the inclusion of non-consecutive patients or the use of non validated scores are among the most frequent causes of under- or over-diagnosis of bronchiectasis in COPD (table2b).

It is important to recognize that the classical criteria for the radiological diagnosis of bronchiectasis (especially the broncho-arterial ratio >1 usually with airway wall thickening)[3] may not apply to patients with other cardiopulmonary diseases or in the elderly. In case of an airway disease, a decrease in the vessel diameter due to hypoxic vasoconstriction or increase in this diameter in the presence of vascular hypertension may lead to under- or over-diagnosis of radiological bronchial dilatation or bronchiectasis[43, 44] (figure 1a). Indeed, almost 20% of healthy elderly subjects have a broncho-arterial ratio >1 in some pulmonary segments without any symptoms of bronchiectasis, usually without increased bronchial wall thickening [45].

Association of bronchiectasis and COPD.

COPD is a physiological diagnosis made in the presence of an appropriate exposure history (mainly tobacco smoking) that in some patients can be associated with airway wall changes[46, 47], whereas bronchiectasis is a radiological diagnosis that in some cases can be associated with poorly-reversible airflow obstruction[48–50]. If there is no significant exposure history, and outside the context of known deficiency such as alpha-1 antitrypsin deficiency, there cannot be an overlap between bronchiectasis and COPD, because such a case does not fulfill the diagnostic criteria of COPD. In this situation, airflow obstruction is best considered one component of bronchiectasis severity. Airflow obstruction is recognized as a severity marker in bronchiectasis, as reflected in severity and prognostic scores such as the Bronchiectasis Severity Index[51] and FACED/E-FACED[52, 53]. A different situation is the development of bronchiectasis in a smoker with COPD.

Although there is no evidence of a causal relationship between COPD and bronchiectasis it seems to be biologically plausible since smoking (or other respiratory exposure) can facilitate chronic bronchial infection and the consequent inflammation may sustain the development of bronchiectasis[54–56] (figure 1b). Very few studies that have recruited random populations of people with COPD or bronchiectasis and carefully assessed subjects for the presence of the other condition; thus it remains unclear whether the presence of both conditions represents a chance association, or whether there is a causal link. The CanCOLD study included healthy adults, smokers with normal lung function and patients with COPD and found a prevalence of bronchiectasis of 19.9% in both healthy individuals and smokers without COPD, and this prevalence increased to 35% in severe COPD. Interestingly this study showed a clear association of bronchiectasis with COPD severity, dyspnoea and poor health status, but not significantly with cough and expectoration[37]. Bronchiectasis in COPD has been proposed as 'clinical phenotype'[13, 14, 57]. A phenotype, in the context of COPD, is defined as a group of features that predict natural history and/or treatment response[58]. Ideally this would be stable over time. Patients with COPD may have more than one phenotype, which may overlap[58]. Irrespective of how overlap arises – chance or true association – the presence of bronchiectasis in COPD is associated with poor outcomes, including mortality. Martínez-García *et al*, for example, reported that bronchiectasis in COPD was associated with increased risk of exacerbations, and was predictive for mortality over 48 months[59]. Meta-analyses[8, 42] of features of overlap versus COPD alone have also demonstrated associations with older age, male gender, more severe airflow obstruction, greater sputum production, isolation of sputum pathogens including *P. aeruginosa,* and greater systemic inflammation. Bronchiectasis has also been associated with alpha-1 antitrypsin deficiency, with the mechanistic link of incompletely-opposed neutrophil elastase activity[60]. However, as with 'usual COPD', the true prevalence of bronchiectasis in populations with alpha-1, and whether this is elevated compared to usual COPD remain controversial[61].

In cohorts with a primary diagnosis of bronchiectasis, the overlap with COPD was associated with a doubling of the risk of mortality, making it the most relevant prognostic co-morbidity after malignancy. In a recent study defining the frequent

exacerbator phenotype in bronchiectasis, patients with co-existing COPD had a 43% increased risk of future exacerbations even after adjustment for prior exacerbation history and other confounders[10, 62].

These data support the view that where clinicians identify patients as having both disorders, prognosis is generally worse.

Therapeutic consequences.

In a significant number of patients with COPD and bronchiectasis, the main clinical manifestations are those typically associated with bronchiectasis: chronic cough and sputum production, chronic bronchial infection and frequent infective exacerbations[8, 42]. In addition to the use of long acting bronchodilators, which are the basis of COPD treatment[47, 63], we need to provide effective treatment for the bronchiectasis. Therefore, the application of recommendations in guidelines for bronchiectasis is also essential for the management of these overlap patients[48–50]. Macrolides have been largely investigated in both bronchiectasis and COPD. Recent European guidelines support their chronic use in selected bronchiectasis patients[49]. The meta-analysis by Donath et al showed that macrolides can significantly reduce the risk of COPD exacerbations (relative risk reduction 37%, RR= 0.63, 95% CI: 0.45-0.87, p-value= 0.005) and updated COPD guidelines suggest use of macrolides for patients suffering multiple exacerbations despite LABA/LAMA/ICS therapy[46, 47]. Caution is, however, warranted since there are no studies specifically in COPD/BE overlap for either macrolides. Macrolides have significant concerns around their use including induction of cardiovascular effects and antibiotic resistance; this is particularly dangerous in case of non-tuberculous mycobacterial infections (reported in up to 10% of COPD patients), due to the increased risk of treatment failure and mortality [64–66].

Inhaled antibiotics are currently not recommended in COPD due to the considerable risk of side effects (bronchospasm) but there is some evidence suggesting that carefully selected patients, such as those with bronchiectasis and/or with chronic *P. aeruginosa* could benefit from this intervention but clearly more research is needed in this field[67, 68].

The risk of acute and chronic bacterial infection implies that special attention must be paid to the use of drugs with possible immunosuppressant activity, such as inhaled corticosteroids (ICS). There are reports indicating that the use of ICS in COPD may be associated with increased bacterial load in the airways[69] and an increased risk of bacterial pneumonia [70]. A Cochrane review published in 2009 concluded that there is insufficient evidence to recommend the routine use of inhaled steroids in adults with stable state bronchiectasis unless specific conditions in which the possible benefits in exacerbation reduction outweigh the risks[48, 49, 71, 72]

ICS are primarily effective in eosinophilic inflammation airways diseases such as usual asthma and should therefore not be used in the majority of bronchiectasis patients that have neutrophilic inflammation[73, 74].

Future directions for research:

It is clear that there are significant knowledge gaps in relation to bronchiectasis-COPD overlap [75]. A consensus for criteria defining radiological and clinical bronchiectasis in COPD patients is needed. The true prevalence of bronchiectasis in these patients could be investigated by analyzing COPD patients from large international cohorts in order to minimize the risk of selection bias and to have a good representation of the COPD population.. Moreover, the prognostic value of bronchiectasis in COPD patients should be confirmed by larger prospective studies.

Ideally, a new method to diagnose bronchiectasis independent of the vessel diameter should be validated. To accomplish this, it would be necessary to measure the distribution of normal airway diameters in the general population and calculate predicted values depending on age, gender, anthropometric variables and airway generation, in a similar way to that in which spirometric parameters are used for the diagnosis of airway obstruction. This measurement would be independent of vessel diameter, and therefore independent of the etiology and respiratory comorbidity. After radiological diagnosis of bronchial dilatation has been established, the diagnosis of bronchiectasis in COPD as an overlap syndrome should only be made if there is a

compatible clinical picture (usually daily productive cough or increase in the volume, viscosity or purulence of the sputum). The presence of bronchial wall thickening as a reflection of bronchial inflammation in an appropriate context could also assist in diagnosis[45].

Another particularly important evidence-gap is the lack of specific biomarkers linking COPD and bronchiectasis, especially those associated with neutrophilic inflammation[76], the possible existence of endotypes related to shared pathophysiological pathways, and genetic and epigenetic alterations leading to changes in the susceptibility to infections and response to treatment[77]. This would answer questions such as why not all patients with COPD present with chronic bronchial infection and/or bronchiectasis.

Better yet would be studies designed to arrest the development and progression of bronchiectasis in COPD, given that this is associated with poor outcomes, and in order to confirm a cause-effect relationship. Longitudinal studies in COPD using repeated imaging techniques over time to identify the development of bronchiectasis and associated factors are needed.

Moreover, studies examining the impact of existing and new interventions in patients with COPD with and without bronchiectasis and chronic bronchial infection are needed. For instance, inhaled corticosteroids have currently little role in the management of bronchiectasis[26–28, 43] but are indicated in some patients with COPD and frequent exacerbations[46, 47]. There is also more evidence needed for the role of macrolides and other anti-inflammatory molecules such us PDE-4 inhibitors in the overlap syndrome, and the wider role of prophylactic antibiotic treatment, either systemic or by inhalation.

Table 1. Characteristics of the studies analyzing the prevalence and outcomes related to the presence of bronchiectasis in COPD patients.

Study (year)	Selection criteria	n	Age (yrs)/gender	Main objective	Bch criteria	Bch prevalence
O´Brien et al (2000)[41]	Primary care diagnosis of COPD with acute exacerbation	110	66.5 58% males	Diagnosis of COPD in primary care	Naidich and Hansell	**29%** Cystic: 15.5% Varicose: 12.5% Tubular 72%
Patel et al (2004)[78]	Stable moderate-to-severe COPD	54	69	Prevalence and extent of BCH and emphysema	Naidich (diagnosis) and Smith (0-4 points grading) Score<2 was considered normal	**50%** 66.7 % Lower lobes
Roche et al (2007)[79]	Hospitalized COPD	118	68.4 (12.1) 74% males	Sputum examination analysis	Bronchi/vessel (diameter)>1	**19.8%**
Garcia-Vidal et al (2009)[80]	Hospitalized COPD (Previous Bch were excluded)	88	72.1 (10) 95% males	Incidence and risk factors for PA	Less than 2 affected segments were considered normal	**52%**
Agusti et al (2010) [81]	ECLIPSE cohort of GOLD II-IV stable COPD (Previous Bch were excluded)	2164	63.4 (7.1) 65% males	Characterization of COPD heterogeneity	No criteria available	**4%** Stage II: **1-2%** Stage III: **3-6%**

						Stage IV: **7-9%**
Bafadhel et al (2011)[82]	Stable COPD (only if previous CT scan)	75	67 (43-88) 58% males	CT scan COPD phenotypes	Naidich (diagnosis) and 0-4 points (grading)	**27%**
Martinez-Garcia et al (2011)[83]	Stable moderate-to-severe COPD. Previous Bch were excluded	92	71.3 (9.3) 99% males	Factor associated with BCH	Naidich More than 1 segment	**57.6%** 34.7% moderate 72.5% severe 90.6%cylindrical 60.4% lower lobes
Arram OA et al (2012)[84]	Moderate-to-severe stable COPD	69	59.4-60.4 95% males	Incidence of BCH	No criteria available	**47.8%** Moderate**31.3%** Severe **62.2%** 82% cylindrical 67% lower lobes 73% bilateral
Stewart JI et al (2012)[85]	Stable COPD GOLD II-IV COPDGene	3752	62.8-65.5 55% males	Prevalence and clinical impact of BCH	Visual assessment	**20.8%** GOLD II: 18.8% GOLD III: 24%

						GOLD IV: 24%
Martinez-Garcia et al (2013)[59]	Stable moderate-to-severe COPD. Previous BCH were excluded	201	70.3 (8.9) 90.5% males	Prognostic value of BCH	Naidich More than 1 segment Bhalla (grading)	**57.2%** 87% cylindrical 81% lower lobes 8.3 Bhalla score
Tulek et al (2013)[86]	Stable COPD (BCH or clinical evidence of BCH were excluded)	80	68 (8) 95% males	Radiological COPD phenotypes	Naidich Modified Bhalla (grading)	**33.8%** -40% in moderate-to-severe patients
Gallego M et al (2014)[87]	Exacerbate severe COPD with exacerbator phenotype	118	69.5 (8.2) Predominantly males	Prevalence and risk factors for PA	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
Gatheral et al (2014)[88]	First hospitalized COPD	406	71 (11) 56% males	Impact of BCH on clinical outcomes	Naidich 0 (absent)-4 severe BCH points (no reference)	**69%** Minor (40%) Mild (29%) Moderate (22%) Severe (8%)

						-Increase with age and male
Jairam PM et al (2015)[89]	COPD without previous exacerbations and CT performed due to non-pulmonary causes)	338	71 (61-76) 54% males	Incidental CT findings and risk of hospitalization or death due to COPD exacerbation	Fleischner Society Criteria (diagnosis) Lobe-based visual grading system (0-3 points per lobe)	**32.5%** Score=1: 14% Score=2: 9% Score>2: 9%
Mao et al (2015)[90]	Stable COPD (only if previous CT scan)	896	66.2 (9.6) 85% males	Prognostic value of BCH	Naidich	**34.7%**
Doria da Silva et al (2016)[91]	Stable COPD (Previous BCH were excluded)	65	64.2 (8.5) 66% males	COPD phenotypes on HRCT	Bhalla system	**33.8%**
Tan et al (2016) [45]	Stable COPD (Canadian cohort)	451	62.8-69 46-50% males	CT abnormalities	Fleischner Society Criteria	**Mild: 14.1%** **Moderate 22.2%** **Severe 35.1%**
Dou et al (2018)[92]	Stable COPD (only if CT scan in previous 12 months)	1739	68.5 (9.7) 79.8% males	Relationship between broncbiectasis and emphysema	Bhalla system	**8.1%**

Footnote: BCH: bronchiectasis; COPD: Chronic obstructive pulmonary disease; HRCT: High-resolution computed tomography; ESR: erythrocyte sedimentation rate; PA: Pseudomonas aeruginosa; CC: Chronic colonization; CPR; C-reactive protein; BMI: Body mass index; PPM: potentially pathogenic microorganism; 6MWT: 6-minute walking test.HRCT: 1-mm collimation at 10-mm intervals from the lung apex to the diaphragm.

Table 2a. Over-diagnosis and under-diagnosis of radiological bronchial dilatation in COPD patients.	
Over-diagnosis of bronchial dilatation	**Under-diagnosis of bronchial dilatation**
-Interstitial lung diseases or emphysema -Healthy elderly[45] -Radiological images mimicking bronchiectasis (cystic diseases)[93, 94] -False bronchiectasis due to hypoxic vasoconstriction[43, 44] -Non-tangential CT slides[93, 94]	-Presence of vascular hypertension increasing vessel size. -CT without high-resolution algorithms from apex to pulmonary bases[93, 94]
Table 2b. **Limitations of study designs to analyze the prevalence of bronchiectasis in COPD patients**	
Over-diagnosis of bronchiectasis	**Under-diagnosis of bronchiectasis**

-Inclusion on non-consecutive patients -Retrospective studies -Inclusion of COPD patients during an exacerbation period - Evidence of publication bias - Inconsistent definitions of bronchiectasis -Inclusion of isolated small cylindrical bronchiectasis in only one pulmonary segment	-Exclusion of previous bronchiectasis -Not using validated radiological scores to the diagnose bronchiectasis -Exclusion of patients with underlying diseases capable of causing bronchiectasis -Inclusion of non-consecutive patients -Performance of CT scan with an objective other than the diagnosis of bronchiectasis (e.g. emphysema quantification)[81] - Evidence of publication bias - Inconsistent definitions of bronchiectasis

OVERLAP ASTHMA AND BRONCHIECTASIS

Asthma and bronchiectasis are often partners of a complex relationship. Despite a different pathophysiology, these two conditions often show similarities (Table 3). In particular, asthma and bronchiectasis have a similar degree of heterogeneity in terms of clinical manifestations and clinical outcomes. Clinical manifestations, such cough, expectoration, dyspnoea, obstructive pattern and wheezing may be similar in these two conditions, as demonstrated by the inclusion of bronchiectasis in the differential diagnosis of asthma in all age groups[95]. Moreover many cases of bronchiectasis due to antibody deficiencies, such common variable immune deficiency (CVID) often show a functional pattern very similar to asthma[96]. However, while airway pathology in asthma is characterized by predominantly eosinophilic airway inflammation, epithelial abnormalities (such as thickening of the sub-epithelial layer and an exaggerated release of various cytokines), smooth muscle proliferation and airway thickening, on the other hand bronchiectasis are mostly characterized by intense neutrophilic inflammation, large-medium bronchial dilatation, epithelial disruption and mucus hyper secretion[95, 97–100][101, 102].

Table 3. Main clinical and functional similarities between asthma and bronchiectasis

Asthma	**Bronchiectasis**
• Chronic respiratory disease with heterogenous clinical manifestations	• Chronic respiratory disease with heterogenous clinical manifestations
• Complex pathophysiology	• Complex pathophysiology
• Chronic airways inflammation o Mostly eosinophilic	• Chronic airways inflammation o Mostly neutrophilic
• Ventilatory disorder o Obstructive o Mostly reversible o	• Ventilatory disorder o Mostly obstructive o Mostly non-reversible
• Exacerbations: marker of disease control o Infectious (viral?) o Non-infectious (allergens, treatment compliance, pollution)	• Exacerbations: marker of disease control o Infectious (bacterial, viral mixed, fungal…) o Non-infectious (?)

A clear causal relationship between the two entities is not well established[26–28, 60] with the potential exception of CVID that can justify a reversible obstructive pattern with wheezing and the development of bronchiectasis as a consequence of pneumonia. The detection of bronchiectasis in many patients with severe asthma has generated the hypothesis of a causative role of bronchial asthma in the development of bronchiectasis[105], however, the detection of bronchiectasis prior to the diagnosis of asthma has also been reported[106]. It is also clear that many patients receive a diagnosis of asthma prior to receiving a diagnosis of bronchiectasis due to initial misdiagnosis. Indeed, in both asthma and bronchiectasis the imbalance between matrix metalloproteinases (MMPs) and tissue inhibitor of MMPs (TIMPs), can lead to

degradation of extracellular matrix, tissue destruction and subsequent remodelling. This imbalance has been clearly described in bronchiectasis but it has also been considered recently in asthma for development of bronchiectasis[107].

Asthma is defined today a “heterogeneous disease”: for instance, the eosinophilic inflammation is present in most but not all patients; similarly allergy is present in only ~50% of patients. In addition, clinical manifestations, natural history and response to treatment can be widely variable; on the other hand acute bronchial reversibility and/or hyper-responsiveness can be observed also in other diseases (i.e. COPD). The only constant feature described across all pheno/endotypes of asthma is the large variability of airway obstruction over time; this is the hallmark of asthma.

Similarly, bronchiectasis are also considered a “heterogeneous disease”, mainly due to different underlying aetiologies such as respiratory infections (pneumonia, tuberculosis), systemic diseases (rheumatoid arthritis, ulcerative colitis), immunological disorders (antibody deficiency, HIV), COPD, and asthma. Accordingly, clinical manifestations, natural history and response to treatment are also very variable[6, 49]. Airway obstruction is described in more than 60% of bronchiectasis patients, although this obstruction is often not reversible[108][19].

The association of asthma and bronchiectasis has been largely described in a variable proportion of patients[4, 17, 49, 105]. Asthma has been reported in 3% to 7% of bronchiectasis patients[109]. On the opposite, bronchiectasis has been reported in 25% to 80% of patients with severe asthma while in mild asthma it is similar to that reported in the general population[17] [17, 110]. Nevertheless airflow obstruction is not required for the diagnosis of bronchiectasis unlike coexisting asthma or COPD.

Accordingly, the overlap between asthma and bronchiectasis may be seen under two different perspectives: 1) bronchiectasis in patients with a confirmed diagnosis of asthma, and 2) asthma, or asthma-like features, in patients with bronchiectasis.

Bronchiectasis in asthma

Bronchiectasis is frequently considered as a consequence of a long-lasting severe uncontrolled asthma.

In patients with asthma**,** the reported prevalence of bronchiectasis is extremely variable depending on patients' selection and type/severity of asthma (Table 4)[7, 16–18, 105, 111–114]. According to the literature, severe asthmatics with frequent exacerbations and patients with non allergic asthma are more likely to show bronchiectasis [7, 114, 115]. Moreover, severe asthmatics with bronchiectasis are often older and show more severe airway obstruction, higher rates of chronic expectoration and infection[110]. A potential mechanism for this association could be a partial immunodeficiency derived from chronic corticosteroid therapy. Indeed, Lujan et al found that bronchiectasis was more prevalent in steroid-dependent asthma patients[111]. Hypogammaglobulinaemia was described in a group of asthma patients in association with an increased risk of bronchiectasis compared to normoglobulinaemia[116]. However, Dimakou and coworkers have recently described bronchiectasis in 67.5% of severe uncontrolled asthma patients. The cases were selected after a complete aetiological investigation and etiologies of bronchiectasis other than asthma were excluded[16]. Interestingly, these severe asthma patients showed pathogens in sputum (mainly *Pseudomonas aeruginosa),* in 22.5% of cases, all in concomitance with bronchiectasis[18].

Although patients with severe asthma and bronchiectasis usually do not report tobacco exposure or neutrophilic airways inflammation, they usually have a poorer prognosis in terms of exacerbations and response to asthma treatment, and often require a therapeutic approach typical of bronchiectasis (long-term antibiotics, chest physiotherapy).

In general, it is sensible to suspect bronchiectasis in severe asthma patients who are poorly responsive to high-dose inhaled corticosteroids and report chronic cough/expectoration, recurrent infectious exacerbations, *Aspergillus* sensitization or high neutrophilia in the sputum.

However, asthma and bronchiectasis can also coexist in the ABPA that is usually characterized by central bronchiectasis, infiltrates, mucus plugging and clinical manifestations of uncontrolled asthma[117, 118]. In the EMBARC database ABPA has been reported in 0% to 11% of all bronchiectasis patients, with a typical decreasing geographic distribution from North to South of Europe[4]. This condition responds fairly well to a specific therapy (systemic corticosteroids and antifungal therapy in some cases), being its identification crucial to achieve control of symptoms and *Aspergillus* sensitization. In consideration of its clinical peculiarities and response to specific treatment we prefer to consider ABPA a separate clinical entity. However, the persistence of bronchiectasis after ABPA may be cause of following exacerbations and bacterial colonization.

Table 4. Prevalence of HRCT bronchiectasis in patients with severe asthma			
Authors	**No. patients**	**Bronchiectasis (BE)**	**Risk factors associated with bronchiectasis**
Bisaccioni at al., Clinics 2009	105	24.8%	not reported
Gupta et al., Chest 2009	467	40%	Disease duration, FEV1/FVC<75%
Menzies et al., Allergy 2011	133	35.3%	Greater airway obstruction, aspergillus fumigatus sensitization
Lujan et al., BioMed RI 2013	50 SD vs 50 NSD	40% vs 12%	age and steroid dependence
Dimakou et al., CRJ 2017	40	67.5%	Sputum, antibiotic courses, bacterial colonization,

Asthma in patients with bronchiectasis.

Although the presence of asthma has been reported in about 3-8% of all bronchiectasis patients (excluding ABPA)[4, 109], the literature on this association is still scarce and the potential influence of asthma on management and prognosis of bronchiectasis is still unclear.

A recent analysis of the EMBARC database showed that asthma had been considered the cause of bronchiectasis in 6.8% of the 7841 patients, but it was also “self-reported” by patients as co-morbidity in 30.5% of all cases[109]. In this study, patients with self-reported asthma have more frequent exacerbations despite similar levels of disease severity. They have less symptoms when clinical stable suggesting a different clinical “phenotype”[109].

Two recent papers have identified asthma as a relevant risk factor for exacerbations of bronchiectasis[15, 119], even despite a lower rate of *P. aeruginosa* infection compared to bronchiectasis patients without asthma[15].

"Asthma-like symptoms" (chest tightness, wheezing, variable resting dyspnoea) may be reported by patients with bronchiectasis, not only during exacerbations but also in stable disease. These patients do not report a history of childhood asthma, although some of them had been erroneously categorised as "asthmatics". The prevalence of "asthma-like symptoms" has not been evaluated in the literature, and strongly depends on the criteria to describe asthma (symptoms alone, acute reversibility of airway obstruction, bronchial hyperresponsiveness, asthma biomarkers like exhaled nitric oxide (NO) or blood/ sputum eosinophils). For instance, Chen et al suggested that exhaled NO could be a good biomarker to identify asthma in bronchiectasis patients but further investigation is needed to validate its use[120]. In a large database of more than 150 patients, almost 20% of them reported a sputum eosinophil percentage greater or equal to 3%, suggesting some degree of airway eosinophilic inflammation[121]. There was no correlation between sputum eosinophilia and acute reversibility of airway obstruction or other clinical "asthma-features", suggesting that this biomarker may not be exclusively related to asthma.

According to these few data, we may argue that patients with bronchiectasis and "asthma features" may represent a different population from those with long asthma history and concomitant bronchiectasis. Likely, biomarkers and long-term variability in pulmonary function over time might be important tools to define the "asthma component" in these patients. This characterization may be relevant for personalising pharmacologic treatment.

Future directions for research

A better characterization of this population is clearly needed. A definition of the asthma-bronchiectasis overlap condition would help to characterize these patients and their specific therapeutic needs. However very heterogeneous data are available so

far. A careful screening of updated diagnostic criteria of asthma, including biological, functional and clinical data, in bronchiectasis patients would likely fill the existing gap. Undoubtedly, considering the huge heterogeneity of bronchiectasis patients, large data set and a representation of different geographic areas are needed to adequately describe asthma in the overall bronchiectasis population.

Likely, the definition of "confirmed" and "potential" asthma-bronchiectasis overlap could facilitate the definition of long-term prognosis and related risk factors. Keistinen in 1997 described prognosis of bronchiectasis as intermediate between COPD and asthma[122], and more recently it has been shown that COPD-bronchiectasis overlap could have a prognosis worse than for COPD or bronchiectasis alone[8, 9, 11]. Unfortunately, there is no information regarding prognosis of asthma-bronchiectasis group.

Additionally, no specific therapies have been defined yet for this potential subset of population. In particular there is need to define: 1) optimal therapy of the airways disease, including bronchodilators, inhaled corticosteroids and/or biologic drugs; 2) appropriate therapy of airways infection, including acute and chronic infections, indications for systemic and inhaled antibiotics, antiviral drugs.

Moreover, the risks related to chronic therapies have not been investigated. In particular, long-term inhaled steroids could potentially increase the risk of fungal and mycobacterial infections; similarly effects of long-term antibiotics (e.g. macrolides) on lung microbiome and immune/inflammatory response should also be investigated.

Finally further investigation of exacerbations (aetiology, clinical presentation, treatment, inflammatory pattern) of asthma-bronchiectasis patients could contribute to improve their management if a different "pheno/endotype" is finally identified.

Upper airway involvement in bronchiectasis

The respiratory tract is a continuum of ciliated epithelium from upper to lower airways. Therefore, it is not surprising that several disease processes, such as CF, PCD, and asthma, involve both upper and lower airways. Chronic rhinosinusitis (CRS) is an

inflammatory condition of the nose and paranasal sinuses, defined as a combination of clinical symptoms (nasal congestion or discharge, facial pain, loss of smell) present for at least 12 weeks together with a finding of inflamed mucosa by endoscopy, or a CT scan showing mucosal changes within the osteomeatal complex and/ or sinuses (Table 4)[123]. CRS is frequent in patients with asthma and allergy[123–126], and the combination of CRS and bronchiectasis is nearly universal in cystic fibrosis (CF)[127] and primary ciliary dyskinesia (PCD)[21, 128]. In these entities, a common mechanism- allergic inflammation or a genetic defect- is affecting both upper and lower airway epithelial function. In bronchiectasis other than CF and PCD, the frequent involvement of upper airways is also well established[21, 128–130]. The prevalence of CRS among patients with bronchiectasis varies from 34%-45% [123, 130–132] to 75% of European patients with bronchiectasis[20, 129, 130] much more common than the 10% prevalence of CRS in the general population[133]. This association suggests that either a common predisposition, or a cause and effect relationship, is shared by CRS and bronchiectasis.

The mechanisms of upper airway involvement in bronchiectasis other than CF and PCD have not been well established. CRS has been found to be more prevalent in idiopathic than in post infectious bronchiectasis[134, 135], leading to the assumption that a common mechanism affecting upper and lower airways is the cause of idiopathic bronchiectasis, while localized inflammation of the lung causes post infectious bronchiectasis with less upper airway involvement. An allergic tendency causing CRS and inflammation of the lower airways has also been suggested[124]. We have found that in patients with bronchiectasis- CRS, peripheral blood eosinophils and IgE are elevated compared to patients with bronchiectasis without CRS with a higher prevalence of concomitant asthma among patients with CRS- BE (14% vs. 6%)[135] This finding needs exploration, given the usual neutrophilic, rather than eosinophilic, airway inflammation in bronchiectasis[136].

Patients with CRS- bronchiectasis are consistently reported to suffer from significantly more exacerbations than bronchiectasis patients without upper airway involvement [21, 129, 135, 137] with a worse quality of life[138]. Comparisons of lung function between patients with bronchiectasis with and without upper airway involvement

have shown contradictory findings [21, 129, 137] with some studies showing worse lung function in patients with CRS involvement[129, 130], others demonstrating the opposite effect[135]. Ramakrishnan et al. compared bacteria present in upper and lower airways of patients with CRS and bronchiectasis. Prevalence of *Pseudomonas aeruginosa* colonization in the lungs and sinuses was 30-35%, and there was 75-93% agreement between cultures from sinuses and from lungs [129]. Concordance between sinus and lung infection has also been found in CF and PCD [139–141], with *Pseudomonas aeruginosa* sinus infection preceding lung infection[140]. It is very plausible given these results that in cases with CRS- bronchiectasis, the sinuses act as a reservoir for bacteria that subsequently infects the bronchi. While the mechanisms for the increased exacerbations are not known, it is possible that some of these exacerbations are driven by rhinosinusitis with post nasal drip causing increased cough.

Treatment of CRS consists of medical and surgical modalities[123]. Application of topical corticosteroids is beneficial in reducing symptoms of nasal secretion and obstruction, and in reducing the size of nasal polyps. Efficacy has been demonstrated for saline irrigation, and irrigation with *anti pseudomonal* antibiotics in colonized patients with CF and PCD has also been used as adjuncts to sinus surgery[141, 142]. In CF, nasal irrigation with rhDNAse has shown improvements in nasal symptom score and lung function [143–145]. Recently, sinonasal surgery has been shown to benefit bronchiectasis symptoms and frequency of exacerbations[146]. Long term treatment with macrolide antibiotics has also been found to reduce symptoms and polyp size [147, 148] but another study of long term azithromycin in CRS did not show such a benefit [149]. According to our own personal experience, inhalation of hypertonic saline through a face mask in patients with CRS- bronchiectasis is beneficial in improving nasal symptoms and mucosal congestion. Sinus surgery, with removal of polyps and restoration of the passage of retained secretions, is beneficial in refractory patients[123]. It is important however, to maintain conservative treatment after surgery in order to prevent relapse of nasal congestion and retained secretions.

<u>Future directions for research:</u>

Although the association of CRS with bronchiectasis is clear, many questions remain as to the pathogenesis and optimal treatment of the various forms of CRS- bronchiectasis. The pathogenesis of the association with CRS in many “idiopathic” and “post infectious” bronchiectasis patients is unclear: is CRS developing into bronchiectasis, is bronchiectasis causing CRS, or is a common mechanism predisposing to both. A possible means of exploring this association may be long term follow up of patients with isolated conditions (CRS alone and bronchiectasis alone) with surveillance of developing the associated condition.

The inflammatory cells present in bronchiectasis airways are dominantly neutrophils, while CRS is mostly mediated by an allergic, eosinophilic inflammation. An important area for research is the nature of the inflammatory process in the airways of bronchiectasis patients with CRS, and whether CRS- bronchiectasis represents a distinct endotype, in which airway inflammation may be eosinophilic rather than neutrophilic. This question may have important implications regarding treatment with anti-inflammatory medications, such as inhaled corticosteroids (ICS). While treatment with ICS has not been established in bronchiectasis[150], individual small studies have found beneficial effects[151–157]. The phenotype of CRS- bronchiectasis may be a distinct subgroup where the effect of ICS may be beneficial. Large scale studies addressing this possibility are needed. These studies should also address the phenotypic variation of CRS- bronchiectasis, as patients with PCD and patients with non PCD- bronchiectasis may have different mechanisms for airway damage, and therefore responses to individual therapies may be quite different.

Table 5: Diagnostic criteria for chronic rhinosinusitis (CRS). From: EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012[123].

Inflammation of the nose and the paranasal sinuses with two or more symptoms for more than 12 weeks:
nasal blockage
obstruction
congestion
nasal discharge
facial pain/pressure
reduction in olfaction
With at least one of the following findings:
nasal polyps
mucopurulent discharge
edema/mucosal obstruction
mucosal changes

CONCLUSIONS

Despite great scientific advances in bronchiectasis of recent years, major knowledge gaps still exist on the different clinical aspects that need to be addressed.

The association of bronchiectasis with COPD and asthma has been described in recent years but still these 'clinical overlaps' need to be investigated in order to unravel specific pathophysiology of these conditions. More importantly, there is need for a specific definition of both conditions of bronchiectasis overlap with COPD and asthma based on radiological, clinical, functional, and biological features. In particular the presence of chronic bronchial obstruction in non-smoking bronchiectasis patients needs to be better defined from a clinical and biological perspective, since a specific treatment could be therefore indicated, as, for instance, in the case of inhaled corticosteroids in patients with eosinophilic airways inflammation. It is likely that specific therapeutic and follow-up interventions are needed to ensure optimal management of these overlap conditions.

The pathogenetic mechanisms underlying the association of bronchiectasis and upper airways diseases are quite known only in presence of PCD. However, the majority of patients presenting with CRS and bronchiectasis do not seem to have ciliary dysfunction and there is a considerable knowledge gap on this subgroup in terms of risk factors, prognosis and therapy.

All these clinical overlap conditions (COPD, asthma and CRS in association with bronchiectasis) seem to have different prognosis but unfortunately scarce information is still available. Moreover, it is unknown whether these different clinical entities share any common pathways in terms of airways inflammation and lung injury or to what extent they can be considered different airways diseases. In particular, it would be crucial in bronchiectasis to identify overlap-specific risk factors contributing to increase susceptibility to infection (both acute and chronic). Only large databases and longitudinal studies can respond to these crucial questions and identify modifiable prognostic factors. Specific biomarkers, more appropriate imaging or functional techniques could hopefully support to follow-up disease progression and contribute to define personalised management.

Finally, we desperately need to define specific therapeutic tools for each overlap disease or “clinical phenotype”, according to underlying inflammatory patterns, risk factors and expected outcomes. As suggested in the past for other chronic respiratory diseases it is possible that all these different conditions can share biological mechanisms leading to development of bronchiectasis but clear differences can be described in terms of clinical, functional, radiological, microbiological, biological aspects that determine distinctive “phenotypes” or overlap syndromes needing targeted interventions[158, 159]. The concept of “precision medicine” would perfectly fit to this field, considering that in bronchiectasis there is a desperate need to define treatable traits of the numerous clinical phenotypes or overlap syndromes described so far. A precise intervention on treatable treats could lead to optimal management of each condition and to improve short and long term outcomes[159].

In conclusion, we believe that only personalised medicine can consistently modify prognosis of bronchiectasis patients and prevent further disease progression through specific interventions directed at treatable treats of each clinical “phenotype or overlap”.

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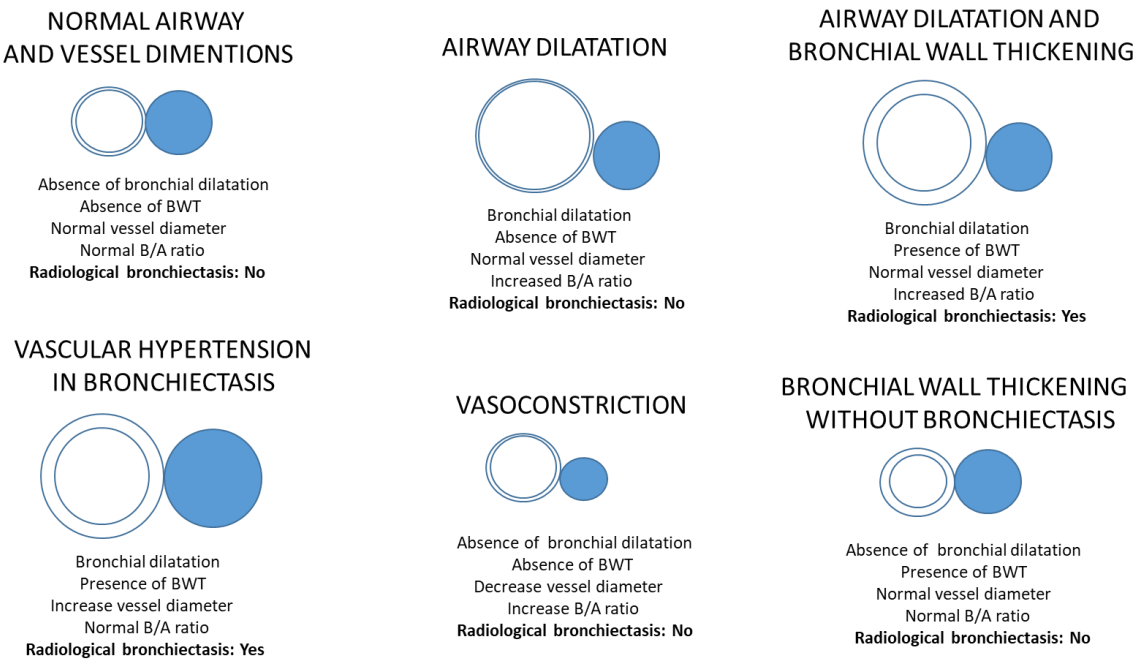
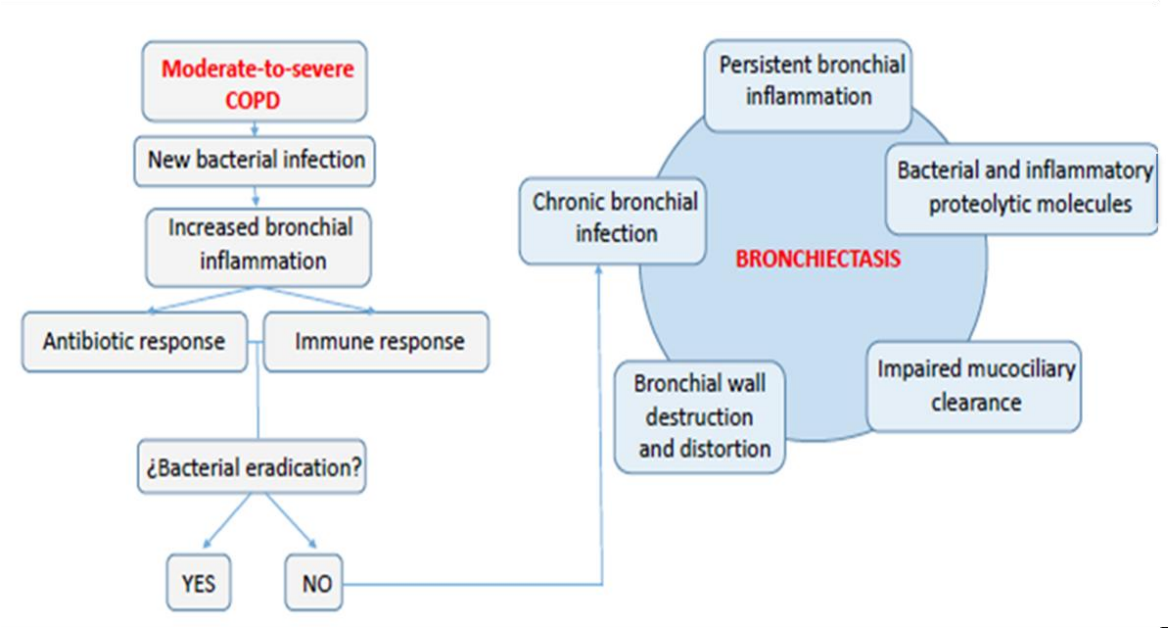
Figure 1a. Broncho-arterial ratio in different conditions.



BWT: Bronchial wall thickening; B/A: broncoarterial

Figure 1b. Pathophysiological pathway linking chronic obstructive pulmonary disease and bronchiectasis.



Fall & Rise hypothesis

Cole's vicious circle

From Martínez-García MA, Maiz L, de la Rosa D. The overlap between COPD and bronchiectasis. Eur Respir Mon 2015; chap 6: 96-109. With permission of ERJ [12].