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

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Bronchiectasis is a heterogeneous disease and frequently overlaps with other chronic airway diseases. Management of these overlap conditions is particularly challenging in terms of diagnosis and therapy, and requires future research. http://ow.ly/snLK30lsrkr

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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 chronic obstructive pulmonary disease (COPD). In addition, 4–72% of patients with severe COPD are found to have radiological bronchiectasis on computed tomography, with similar frequencies (20–30%) now being reported in cohorts with severe or uncontrolled asthma. Co-diagnosis of bronchiectasis with another airway disease is associated with increased lung inflammation, frequent exacerbations, worse lung function and higher mortality. In addition, many patients with all three disorders have chronic rhinosinusitis and upper airway disease, resulting in a complex "mixed airway" phenotype.

The management of asthma, bronchiectasis, COPD and upper airway diseases has traditionally been outlined in separate guidelines for each individual disorder. Recognition that the majority of patients have one or more overlapping pathologies requires that we re-evaluate 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.

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Introduction

Owing to increasing knowledge and awareness, bronchiectasis is not considered a rare condition but a relevant chronic lung disease characterised by permanent bronchial damage and a broad spectrum of chronic respiratory and systemic symptoms [1]. From a radiological perspective, the most accepted diagnostic criteria were defined by NAIDICH *et al.* [2] using a number of direct signs (broncho-arterial ratio >1, lack of bronchial tapering, visualisation of peripheral bronchi within 1 cm of the costal pleura in 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 the bronchiectasis population is its heterogeneity. Patients present with bronchiectasis at variable ages (from early life to older age), have a varied symptom burden (from intermittent dry cough to daily bronchorrhea and frequent exacerbations) and have different prognoses 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 some pathological conditions such as associated respiratory diseases (*e.g.* chronic obstructive pulmonary disease (COPD), asthma, allergic bronchopulmonary aspergillosis (ABPA), sinusitis) or systemic inflammatory diseases (*e.g.* rheumatoid arthritis) [7–12]. Some recent studies suggest that bronchiectasis and COPD coexist in 20–60% of cases [8], and coexisting disease can result in increased symptom burden, a reduced therapeutic arsenal and a worse prognosis compared to COPD or bronchiectasis alone [8, 9, 13, 14]. Unfortunately, it is not 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 the prevention of disease progression.

In recent years, the association between asthma and bronchiectasis has shown potentially specific features in terms of age, clinical presentation, risk of exacerbations and diagnostic and therapeutic options [4, 7, 15]. Unfortunately, there is still limited information on the prognosis of asthma–bronchiectasis overlap, although it has been suggested that patients with severe asthma with bronchiectasis may have a worse prognosis (more symptoms and exacerbations) than asthma patients without bronchiectasis [16–18].

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 treatment of ABPA are characteristic and specific, unlike other bronchiectasis subgroups. This suggests that ABPA is a specific clinical entity rather than an overlap between two different conditions.

Up to 75% of bronchiectasis patients may have upper airway disease and present with severe daily symptoms of nasal congestion, facial pain and/or loss of smell [20]. Primary ciliary dyskinesia (PCD) is a frequent cause of chronic rhinosinusitis (CRS) and bronchiectasis, but rhinosinusitis is relatively frequent in bronchiectasis even in the 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 factor in the mechanism of airway disease is the nature of the bronchial inflammatory process. In bronchiectasis, inflammation is predominated by neutrophils, with elevated levels of interleukin-8 (IL-8) [6, 22–25]. In a study exploring inflammatory cells in the sputum of patients with bronchiectasis, neutrophils predominated over eosinophils, with large variance between patients: the median neutrophil percentage was 79% (range 1.5–98%) and eosinophil percentage was 0.8% (range 0–70%) [23]. In this cohort, 26% of patients had upper airway involvement and 16% had airway reversibility. Elevated neutrophil levels 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]. Levels of inflammatory mediators in the sputum of bronchiectasis were also found to be heterogeneous, with increased levels of IL-8, IL-13, tumour necrosis factor-α (TNF-α) and IL-17, as well as elevated levels of the type 2 mediator IL-4 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 aetiologies [6]. Inflammation is heterogeneous in patients with asthma and CRS, but the majority have an eosinophilic, type 2 T helper cell-mediated inflammation [26]. Similarly, in COPD there is evidence for neutrophil-mediated inflammation, but it has recently been suggested that sputum eosinophilia is associated with more exacerbations. In view of the heterogeneity of airway inflammation in bronchiectasis, it is possible that different inflammatory profiles explain the differences in clinical phenotypes and overlapping airway diseases.

In addition to these chronic inflammatory diseases, gastro-oesophageal reflux disease (GERD) is also associated with bronchiectasis, particularly in the presence of nontuberculous mycobacterial (NTM)

infection, although a causal relationship has not been demonstrated [27, 28]. The hypothesis is that recurrent gastro-oesophageal reflux could irritate upper airways, causing bronchial hyperresponsiveness and lung infections such as aspiration pneumonia or NTM infection, consequently leading to bronchiectasis. It does seems that GERD could worsen the symptoms of bronchiectasis and a Korean group suggested that treatment with proton-pump inhibitors in bronchiectasis patients with a high body mass index could improve lung function [29]. However, the same association between GERD and worse respiratory symptoms can be found for asthma, CRS and COPD [30, 31]. Although the association between GERD and all these chronic airway diseases is clear, a causal connection has not yet been established and further investigation considering potential confounding factors is surely needed.

In addition, it is worth remembering that cystic fibrosis (CF) is also a cause of bronchiectasis but, owing to peculiarities in terms of its pathophysiology (a 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 causes bronchiectasis is PCD. This is a rare condition whose genetics and pathophysiology are still not fully known. Typically, PCD patients show sinus and ear involvement, aside from bronchiectasis, and a variable combination of fertility disorders and, in rare cases, situs inversus [21, 35].

In the face of the heterogeneity of bronchiectasis, it is crucial that the pathophysiological determinants, clinical outcomes and prognostic factors of specific subgroups or phenotypes are investigated 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-characterised 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 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 a few prevalence estimates for this association (table 1). However, despite the possibility of the 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, albeit ranging from 4% to 72% [8, 42]. There may be several reasons for this wide range of prevalence: the presence of vascular hypertension frequently results in misdiagnosis and computed tomography (CT) without high-resolution algorithms is the main cause of under-diagnosis of bronchiectasis. In contrast, erroneous diagnosis (over-diagnosis) of bronchiectasis in COPD may be caused by, for example, the presence of bronchial dilatations in healthy elderly individuals, interstitial lung disease or emphysema usually without bronchial wall thickening (table 2). Limitations in study design also account for the misdiagnosis of bronchiectasis in COPD. The retrospective design of some studies, the inclusion of non-consecutive patients and the use of non-validated scores are among the most frequent causes of under- or over-diagnosis of bronchiectasis in COPD (table 3).

It is important to recognise that the classical criteria for the radiological diagnosis of bronchiectasis (especially a broncho-arterial ratio >1, usually with airway wall thickening) [3] may not apply to patients with other cardiopulmonary diseases or to elderly patients. In cases of airway disease, a decrease in the vessel diameter due to hypoxic vasoconstriction or an increase in this diameter in the presence of vascular hypertension may lead to under- or over-diagnosis of radiological bronchial dilatation or bronchiectasis (figure 1a) [43, 44]. 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 is associated with airway wall changes [46, 47]. Bronchiectasis is a radiological diagnosis that in some cases is associated with poorly reversible airflow obstruction [48–50]. If there is no significant exposure history, and outside the context of a known deficiency such as α_1-antitrypsin deficiency, there cannot be an overlap between bronchiectasis and COPD, because such a case does not fulfil the diagnostic criteria of COPD. In this situation, airflow obstruction is best considered one component of bronchiectasis severity. Airflow obstruction is recognised as a severity marker in

TABLE 1 Characteristics of the studies analysing the prevalence and outcomes related to the presence of bronchiectasis in COPD patients

Study	Selection criteria	n	Age years[#]	Male sex %	Main objective	BCH criteria	BCH prevalence %
O'Brien *et al.*, 2000 [41]	Primary care diagnosis of COPD with acute exacerbation	110	66.5	58	Diagnosis of COPD in primary care	Naidich and Hansell	29 Cystic: 15.5 Varicose: 12.5 Tubular: 72
Patel *et al.*, 2004 [51]	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 Lower lobes: 66.7
Roche *et al.*, 2007 [52]	Hospitalised COPD	118	68.4±12.1	74	Sputum examination analysis	Bronchi/vessel (diameter) >1	19.8
Garcia-Vidal *et al.*, 2009 [53]	Hospitalised COPD (previous BCH were excluded)	88	72.1±10	95	Incidence and risk factors for PA	<2 affected segments were considered normal	52
Agusti *et al.*, 2010 [54]	ECLIPSE cohort of GOLD II–IV stable COPD (previous BCH were excluded)	2164	63.4±7.1	65	Characterisation of COPD heterogeneity	No criteria available	4 Stage II: 1–2 Stage III: 3–6 Stage IV: 7–9
Bafadhel *et al.*, 2011 [55]	Stable COPD (only if previous CT scan)	75	67 (43–88)[¶]	58	CT scan COPD phenotypes	Naidich (diagnosis) and 0–4 points (grading)	27
Martínez-García *et al.*, 2011 [56]	Stable moderate-to-severe COPD (previous BCH were excluded)	92	71.3±9.3	99	Factors associated with BCH	Naidich >1 segment	57.6 Moderate: 34.7 Severe: 72.5 Cylindrical: 90.6 Lower lobes: 60.4
Arram *et al.*, 2012 [57]	Moderate-to-severe stable COPD	69	59.4–60.4[+]	95	Incidence of BCH	No criteria available	47.8 Moderate: 31.3 Severe: 62.2 Cylindrical: 82 Lower lobes: 67 Bilateral: 73
Steward and Maselli, 2012 [58]	Stable COPD GOLD II–IV COPDGene	3752	62.8–65.5[§]	55	Prevalence and clinical impact of BCH	Visual assessment	20.8 GOLD II: 18.8 GOLD III: 24 GOLD IV: 24
Martínez-García *et al.*, 2013 [59]	Stable moderate-to-severe COPD (previous BCH were excluded)	201	70.3±8.9	90.5	Prognostic value of BCH	Naidich >1 segment Bhalla (grading)	57.2 Cylindrical: 87 Lower lobes: 81 Bhalla score: 8.3
Tulek *et al.*, 2013 [60]	Stable COPD (BCH or clinical evidence of BCH were excluded)	80	68±8	95	Radiological COPD phenotypes	Naidich Modified Bhalla (grading)	33.8 Moderate-to-severe patients: 40

Continued

TABLE 1 Continued

Study	Selection criteria	n	Age years[#]	Male sex %	Main objective	BCH criteria	BCH prevalence %
Gallego *et al.*, 2014 [61]	Exacerbate severe COPD with exacerbator phenotype	118	69.5±8.2	Predominantly male	Prevalence and risk factors for PA	Naidich (diagnosis) and Smith (grading) Score⩽1 was considered normal	47 Lower lobes only: 52 >4 lobes: 25 BCH score: 4.2
Gatheral *et al.*, 2014 [62]	First hospitalised COPD	406	71±11	56	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 *et al.*, 2015 [63]	COPD without previous exacerbations CT performed due to non-pulmonary causes)	338	71 (61–76)[f]	54	Incidental CT findings and risk of hospitalisation 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 [64]	Stable COPD (only if previous CT scan)	896	66.2±9.6 85% males		Prognostic value of BCH	Naidich	34.7
da Silva *et al.*, 2016 [65]	Stable COPD (previous BCH were excluded)	65	64.2±8.5	66	COPD phenotypes on HRCT	Bhalla system	33.8
Tan *et al.*, 2016 [45]	Stable COPD (Canadian cohort)	451	62.8–69[§]	46–50	CT abnormalities	Fleischner Society Criteria	Mild: 14.1 Moderate: 22.2 Severe: 35.1
Dou *et al.*, 2018 [66]	Stable COPD (only if CT scan in previous 12 months)	1739	68.5±9.7	79.8	Relationship between bronchiectasis and emphysema	Bhalla system	8.1

BCH: bronchiectasis; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HRCT: high-resolution computed tomography; PA: *Pseudomonas aeruginosa*. [#]: data presented as mean±SD, unless otherwise indicated; [¶]: mean (range); [+]: interquartile range; [§]: range from four different compared groups; [f]: median (interquartile range).

TABLE 2 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	Presence of vascular hypertension increasing vessel size
Healthy elderly [45]	CT without high-resolution algorithms from apex to pulmonary bases [75, 76]
Radiological images mimicking bronchiectasis (cystic diseases) [75, 76]	
False bronchiectasis due to hypoxic vasoconstriction [43, 44]	
Non-tangential CT slides [75, 76]	

COPD: chronic obstructive pulmonary disease; CT: computed tomography.

bronchiectasis, as reflected in severity and prognostic scores such as the Bronchiectasis Severity Index [67] and FACED/E-FACED [68, 69]. A different situation would be the development of bronchiectasis in a smoker with COPD, which would be considered an overlap.

Although there is no evidence for a causal relationship between COPD and bronchiectasis, it seems to be biologically plausible because smoking (or other respiratory exposure) can facilitate chronic bronchial infection and the consequent inflammation may sustain the development of bronchiectasis (figure 1b) [70–72]. Very few studies 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 [45] 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. This prevalence increased to 35% in severe COPD. This study showed a clear association between bronchiectasis and COPD severity, dyspnoea and poor health status, but no significant association with cough and expectoration [37]. Bronchiectasis in COPD has been proposed as a clinical phenotype [13, 14, 73]. A phenotype, in the context of COPD, is defined as a group of features that predict the natural history and/or treatment response [74]. Ideally this would be stable over time. Patients with COPD may have more than one phenotype, which may overlap [74]. Irrespective of how overlap arises, *via* chance or as a true association, the presence of bronchiectasis in COPD is associated with poor outcomes, including mortality. Martínez-García *et al.* [59], for example, reported that bronchiectasis in COPD was associated with an increased risk of exacerbations, and was predictive for mortality over 48 months. Meta-analyses [8, 42] of features of overlap *versus* COPD alone have also demonstrated associations with older age, male sex, more severe airflow obstruction, greater sputum production, isolation of sputum pathogens (including *P. aeruginosa*) and greater systemic inflammation. Bronchiectasis has also been associated with α_1-antitrypsin deficiency, with the mechanistic link of incompletely opposed neutrophil elastase activity [77]. However, as with "usual COPD", the true prevalence of bronchiectasis in populations with α_1-antitrypsin deficiency, and whether this is elevated compared to usual COPD, remains controversial [78].

In cohorts with a primary diagnosis of bronchiectasis, the overlap with COPD is associated with a doubling of the risk of mortality, making it the most relevant prognostic comorbidity after malignancy. In

TABLE 3 Limitations of study designs to analyse the prevalence of bronchiectasis in COPD patients

Over-diagnosis of bronchiectasis	Under-diagnosis of bronchiectasis
Inclusion of non-consecutive patients	Exclusion of previous bronchiectasis
Retrospective studies	Not using validated radiological scores to diagnose bronchiectasis
Inclusion of COPD patients during an exacerbation period	Exclusion of patients with underlying diseases capable of causing bronchiectasis
Evidence of publication bias	Inclusion of non-consecutive patients
Inconsistent definitions of bronchiectasis	Performance of CT scan with an objective other than the diagnosis of bronchiectasis (*e.g.* emphysema quantification) [54]
Inclusion of isolated small cylindrical bronchiectasis in only one pulmonary segment	Evidence of publication bias
	Inconsistent definitions of bronchiectasis

COPD: chronic obstructive pulmonary disease; CT: computed tomography.

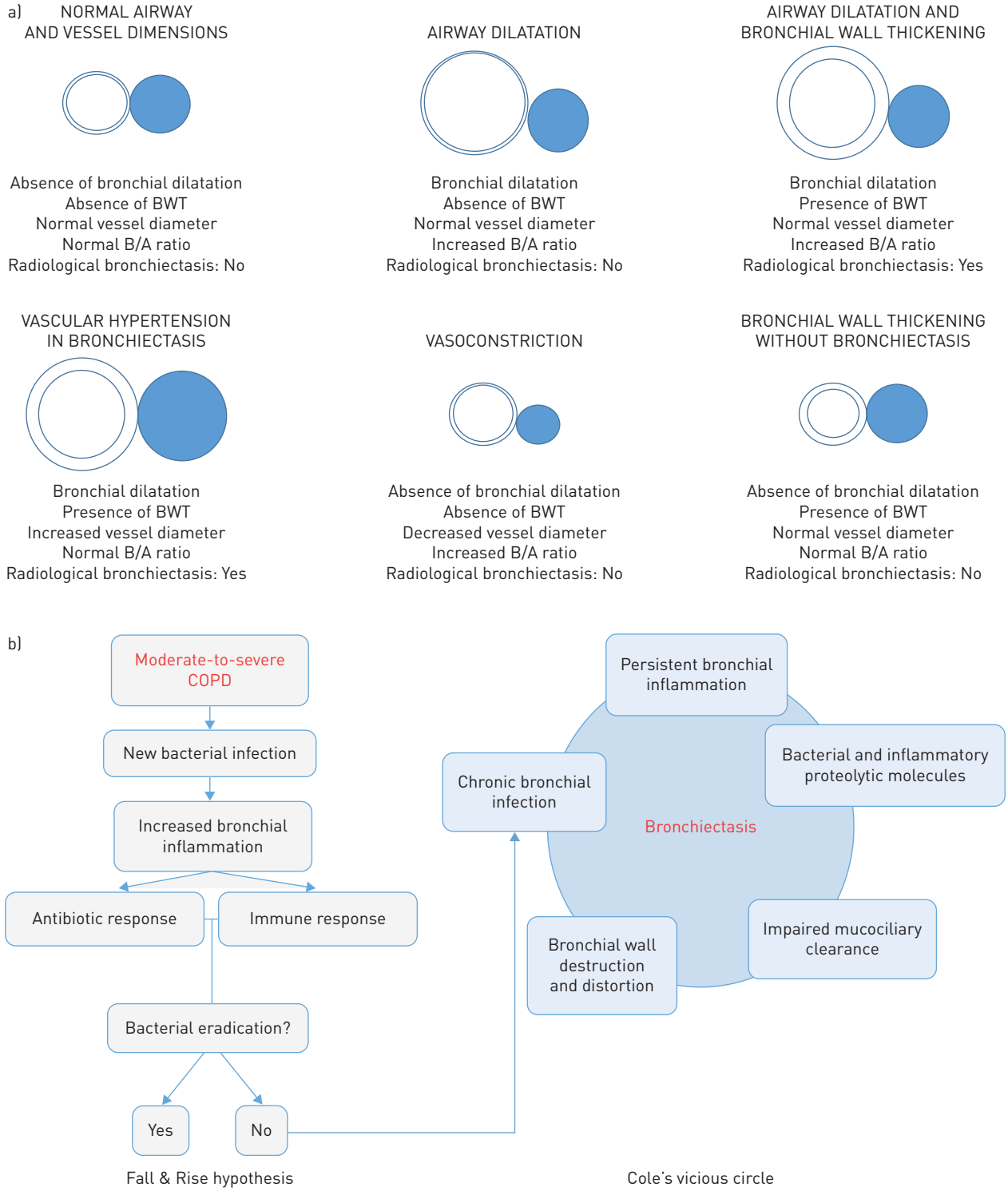

FIGURE 1 a) Broncho-arterial ratio (B/A) in different conditions. BWT: bronchial wall thickening. b) Pathophysiological pathway linking chronic obstructive pulmonary disease (COPD) and bronchiectasis. Reproduced from [14] with permission.

a recent study defining the frequent exacerbator phenotype in bronchiectasis, patients with coexisting COPD had a 43% increased risk of future exacerbations even after adjustment for prior exacerbation history and other confounders [10, 79].

These data support the view that patients identified as having both disorders generally have a worse prognosis.

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, 80], 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 investigated in both bronchiectasis and COPD. Recent European guidelines support their chronic use in selected bronchiectasis patients [49]. A meta-analysis by Donath *et al.* [81] showed that macrolides can significantly reduce the risk of COPD exacerbations (relative risk reduction 37%, relative risk 0.63, 95% CI 0.45–0.87, p=0.005) and updated COPD guidelines suggest using macrolides for patients with multiple exacerbations despite long-acting beta agonists/long-acting muscarinic antagonists/inhaled corticosteroids (ICS) [46, 47]. Caution is, however, warranted because there are no studies specifically in COPD–bronchiectasis overlap for either macrolide. There are significant concerns around the use of macrolides, including the induction of cardiovascular effects and antibiotic resistance; this is particularly dangerous in nontuberculous mycobacterial infections (reported in up to 10% of COPD patients) owing to the increased risk of treatment failure and mortality [82–84].

Inhaled antibiotics are currently not recommended in COPD owing 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* infection, could benefit from this intervention but clearly more research is needed in this field [85, 86].

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 ICS. There are reports indicating that the use of ICS in COPD may be associated with increased bacterial load in the airways [87] and an increased risk of bacterial pneumonia [88]. A Cochrane review published in 2009 [89] concluded that there is insufficient evidence to recommend the routine use of inhaled steroids in adults with stable state bronchiectasis except for in specific conditions in which the possible benefits in exacerbation reduction outweigh the risks [48, 49, 89, 90].

ICS are primarily effective in eosinophilic inflammation airway diseases such as usual asthma and should therefore not be used in the majority of bronchiectasis patients who have neutrophilic inflammation [91, 92].

Future directions for research

It is clear that there are significant knowledge gaps in relation to COPD–bronchiectasis overlap [93]. 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 analysing COPD patients from large international cohorts in order to minimise the risk of selection bias and to have 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, the distribution of normal airway diameters must be measured in the general population and predicted values calculated depending on age, sex, anthropometric variables and airway generation, in a similar way to that in which spirometric parameters are used to diagnose airway obstruction. This measurement would be independent of vessel diameter, and therefore independent of aetiology and respiratory comorbidities. After establishing the radiological diagnosis of bronchial dilatation, bronchiectasis in COPD as an overlap syndrome should only be diagnosed 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].

Other particularly important evidence gaps are the lack of specific biomarkers linking COPD and bronchiectasis, especially those associated with neutrophilic inflammation [94], 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 [95]. These 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 firstly this is associated with poor outcomes, and secondly this would allow a cause–effect relationship to be confirmed. Longitudinal studies in COPD are needed that use repeated imaging techniques over time to identify the development of bronchiectasis and associated factors.

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 currently have 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 as PDE-4 inhibitors in the overlap syndrome, and the wider role of prophylactic antibiotic treatment, either systemic or by inhalation.

Overlap asthma and bronchiectasis

Asthma and bronchiectasis are often partners in a complex relationship. Despite a different pathophysiology, these two conditions often show similarities (table 4). In particular, asthma and bronchiectasis have a similar degree of heterogeneity in terms of clinical manifestations and clinical outcomes. Clinical manifestations, such as 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 [96]. Moreover, many cases of bronchiectasis due to antibody deficiencies, such as common variable immune deficiency (CVID), show a functional pattern very similar to that of asthma [97]. However, while airway pathology in asthma is characterised 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, bronchiectasis is mostly characterised by intense neutrophilic inflammation, large to medium bronchial dilatation, epithelial disruption and mucus hyper-secretion [96, 98–103].

A clear causal relationship between the two entities is not well established [26–28, 77], with the potential exception of CVID in which a reversible obstructive pattern with wheezing and the development of bronchiectasis can be a consequence of pneumonia. The detection of bronchiectasis in many patients with severe asthma has generated the hypothesis that bronchial asthma has a causative role in the development of bronchiectasis [104]; however, the detection of bronchiectasis prior to the diagnosis of asthma has also been reported [105]. 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 inhibitors of MMPs can lead to the 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 the development of bronchiectasis [106].

Asthma is a heterogeneous disease: *e.g.* eosinophilic inflammation is present in most but not all patients, and allergy is present in only ∼50% of patients. In addition, clinical manifestations, natural history and response to treatment can vary widely; however, acute bronchial reversibility and/or hyperresponsiveness can also be observed in other diseases (*e.g.* COPD). The only constant feature described across all pheno- and endotypes of asthma is the large variability of airway obstruction over time; this is the hallmark of asthma.

Similarly, bronchiectasis is 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, the clinical manifestation, natural history and response to treatment are also varied [6, 49]. Airway obstruction is described in >60% of bronchiectasis patients, although this obstruction is often not reversible [19, 107].

The association of asthma and bronchiectasis has been described in a variable proportion of patients [4, 17, 49, 104]. Asthma has been reported in 3–8% of bronchiectasis patients [108]. Bronchiectasis has

TABLE 4 Main clinical and functional similarities between asthma and bronchiectasis

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

been reported in 25–80% of patients with severe asthma, whereas in mild asthma the prevalence is similar to that reported in the general population [17, 109]. Nevertheless, airflow obstruction is not required for the diagnosis of bronchiectasis, unlike coexisting asthma or COPD.

Accordingly, the overlap between asthma and bronchiectasis can be viewed in two ways: 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 to be a consequence of long-lasting, severe, uncontrolled asthma. In patients with asthma, the reported prevalence of bronchiectasis is extremely variable, depending on patient selection and type/severity of asthma (table 5) [7, 16–18, 104, 110–113]. According to the literature, patients with severe asthma with frequent exacerbations and patients with non-allergic asthma are more likely to have bronchiectasis [7, 113, 114]. Moreover, patients with severe asthma with bronchiectasis are often older and show more severe airway obstruction, and higher rates of chronic expectoration and infection [109]. A potential mechanism for this association is a partial immunodeficiency derived from chronic corticosteroid therapy. Indeed, Luján *et al.* [110] found that bronchiectasis was more prevalent in patients with steroid-dependent asthma. Hypogammaglobulinaemia was described in a group of asthma patients in association with an increased risk of bronchiectasis compared to normoglobulinaemia [115]. However, Dimakou *et al.* [16] recently described bronchiectasis in 67.5% of patients with severe uncontrolled asthma. The cases were selected after a complete aetiological investigation and aetiologies of bronchiectasis other than asthma were excluded. These patients with severe asthma showed pathogens in sputum (mainly *P. aeruginosa)* in 22.5% of cases, all concomitant with bronchiectasis [18].

Although patients with severe asthma and bronchiectasis usually do not report tobacco exposure or neutrophilic airway 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 patients with severe asthma who show a poor response to high-dose ICS and report chronic cough/expectoration, recurrent infectious exacerbations, *Aspergillus* sensitisation or neutrophilia in the sputum.

Asthma and bronchiectasis can also coexist in ABPA, which is usually characterised by central bronchiectasis, infiltrates, mucus plugging and clinical manifestations of uncontrolled asthma [116, 117]. In the EMBARC database, ABPA has been reported in 0–11% of all bronchiectasis patients, with a typical decreasing geographic distribution from the north to the south of Europe [4]. This condition responds fairly well to a specific therapy (systemic corticosteroids and antifungal therapy in some cases), with its identification crucial to achieving control of symptoms and *Aspergillus* sensitisation. In terms of its clinical peculiarities and response to specific treatment, ABPA can be considered a separate clinical entity. However, the persistence of bronchiectasis after ABPA may cause subsequent exacerbations and bacterial colonisation.

Asthma in patients with bronchiectasis

Although the presence of asthma has been reported in about 3–8% of all bronchiectasis patients (excluding ABPA) [4, 108], literature on this association is still scarce and the potential influence of asthma on the management and prognosis of bronchiectasis is unclear.

TABLE 5 Prevalence of high-resolution computed tomography-diagnosed bronchiectasis in patients with severe asthma

Study	Subjects n	BCH prevalence %	Risk factors associated with BCH
Bisaccioni *et al.*, 2009 [104]	105	24.8	NR
Gupta *et al.*, 2009 [111]	467	40	Disease duration, $FEV_1/FVC < 75\%$
Menzies *et al.*, 2011 [17]	133	35.3	Greater airway obstruction, *Aspergillus fumigatus* sensitisation
Luján *et al.*, 2013 [110]	50 SD *versus* 50 NSD	40 *versus* 12	age and steroid dependence
Dimakou *et al.*, 2017 [18]	40	67.5	Sputum, antibiotic courses, bacterial colonisation

BCH: bronchiectasis; NR: not reported; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SD: steroid-dependent; NSD: non steroid-dependent.

A recent analysis of the EMBARC database showed that asthma was considered the cause of bronchiectasis in 6.8% of 7841 patients, but it was also "self-reported" by patients as a comorbidity in 30.5% of all cases [108]. In this study, patients with self-reported asthma had more frequent exacerbations despite similar levels of disease severity. They had fewer symptoms when clinically stable, suggesting a different clinical phenotype [108].

Two recent papers identified asthma as a relevant risk factor for exacerbations of bronchiectasis [15, 118], despite a lower rate of *P. aeruginosa* infection compared to bronchiectasis patients without asthma [15].

"Asthma-like symptoms" (*e.g.* 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 in bronchiectasis has not been evaluated in the literature, and strongly depends on the criteria used to describe asthma (*e.g.* 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.* [119] suggested that exhaled NO could be a good biomarker to identify asthma in bronchiectasis patients but further investigation is needed to validate its use. In a large database of >150 patients, almost 20% of them had a sputum eosinophil percentage ⩾3%, suggesting some degree of airway eosinophilic inflammation [23]. 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 could argue that patients with bronchiectasis and asthma features may represent a different population from those with a long asthma history and concomitant bronchiectasis. It is likely that biomarkers and long-term variability in pulmonary function over time might be important tools to define the "asthma component" in these patients. This characterisation may be relevant for personalising pharmacological treatment.

Future directions for research

A better characterisation of the population with asthma–bronchiectasis overlap is clearly needed. Defining this overlap condition would help to characterise these patients and their specific therapeutic needs. However, the data available so far are very heterogeneous. 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, a large data set and representation of different geographic areas are needed to adequately describe asthma in the overall bronchiectasis population.

Defining "confirmed" and "potential" asthma–bronchiectasis overlap could help define long-term prognosis and related risk factors. In 1997, Keistinen *et al.* [120] described the prognosis of bronchiectasis as intermediate between COPD and asthma; more recently, it has been shown that COPD–bronchiectasis overlap could have a worse prognosis than for COPD or bronchiectasis alone [8, 9, 11]. Unfortunately, there is no information regarding the prognosis of patients with asthma–bronchiectasis overlap.

No specific therapies have yet been defined for this potential subset of the population. In particular, the following need to be defined: 1) optimal therapy of the airway disease, including bronchodilators, ICS and/or biologic drugs; and 2) appropriate therapy of airway infection, including acute and chronic infections, indications for systemic and inhaled antibiotics, and 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 the lung microbiome and immune/inflammatory response should also be investigated.

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

Upper airway involvement in bronchiectasis

The respiratory tract is a continuum of ciliated epithelium from the upper to the lower airways. Therefore, it is not surprising that several disease processes, such as CF, PCD and asthma, involve both upper and lower airways. 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 6) [121]. CRS is frequent in patients with

TABLE 6 Diagnostic criteria for chronic rhinosinusitis

Inflammation of the nose and the paranasal sinuses with two or more symptoms for >12 weeks:
Nasal blockage
Obstruction
Congestion
Nasal discharge
Facial pain/pressure
Reduction in olfaction
With at least one of the following findings on endoscopy or CT:
Nasal polyps
Mucopurulent discharge
Oedema/mucosal obstruction
Mucosal changes

CT: computed tomography. Adapted from [121]

asthma and allergy [121–124], and the combination of CRS and bronchiectasis is nearly universal in CF [125] and PCD [21, 126]. In these entities, a common mechanism, *e.g.* allergic inflammation or a genetic defect, affects both upper and lower airway epithelial function. In bronchiectasis other than CF and PCD, the frequent involvement of the upper airways is also well established [21, 126–128]. The prevalence of CRS among patients with bronchiectasis varies from 34% to 75% in European patients with bronchiectasis [20, 121, 127–130], and is much more common than the 10% prevalence of CRS in the general population [131]. 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 is more prevalent in idiopathic than in postinfectious bronchiectasis [132, 133], leading to the assumption that a common mechanism affecting the upper and lower airways causes idiopathic bronchiectasis, whereas localised inflammation of the lung causes postinfectious bronchiectasis with less upper airway involvement. An allergic tendency causing CRS and inflammation of the lower airways has also been suggested [122]. We have found that peripheral blood eosinophils and IgE are elevated in patients with CRS–bronchiectasis compared to in patients with bronchiectasis without CRS, with a higher prevalence of concomitant asthma among patients with CRS–bronchiectasis (14% *versus* 6%) [133]. This finding needs exploration, given the usual neutrophilic, rather than eosinophilic, airway inflammation in bronchiectasis [134].

Patients with CRS–bronchiectasis are consistently reported to have significantly more exacerbations than bronchiectasis patients without upper airway involvement [21, 127, 133, 135], with a worse quality of life [136]. Comparisons of lung function between patients with bronchiectasis with and without upper airway involvement have shown contradictory findings [21, 127, 135], with some studies showing worse lung function in patients with CRS involvement [127, 128] and others demonstrating the opposite effect [133]. Ramakrishnan *et al.* [127] compared bacteria present in the upper and lower airways of patients with CRS and bronchiectasis. The prevalence of *P. aeruginosa* colonisation in the lungs and sinuses was 30–35%, and there was 75–93% agreement between cultures from sinuses and lungs. Concordance between sinus and lung infection has also been found in CF and PCD [137–139], with *P. aeruginosa* sinus infection preceding lung infection [138]. It is very plausible given these results that in cases with CRS–bronchiectasis, the sinuses act as a reservoir for bacteria that subsequently infect 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 [121]. Applying 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 colonised patients with CF and PCD has also been used as an adjunct to sinus surgery [139, 140]. In CF, nasal irrigation with recombinant human DNAse has resulted in improvements in nasal symptom score and lung function [141–143]. Recently, sinonasal surgery has been shown to improve bronchiectasis symptoms and decrease the frequency of exacerbations [144]. Long-term treatment with macrolide antibiotics has also been found to reduce symptoms and polyp size [145, 146] but another study of long-term azithromycin in CRS did not show such a benefit [147]. 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 patients with refractory disease [121]. It is important, however, to maintain conservative treatment after surgery in order to prevent the relapse of nasal congestion and retained secretions.

Future directions for research

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 patients with idiopathic and postinfectious bronchiectasis 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 the long-term follow-up of patients with isolated conditions (CRS alone and bronchiectasis alone) to observe the development of the associated condition.

The inflammatory cells present in bronchiectasis airways are dominantly neutrophils, whereas 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 ICS. While treatment with ICS has not been established in bronchiectasis [148], individual small studies have found beneficial effects [149–155]. The phenotype of CRS–bronchiectasis may be a distinct subgroup in which 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, because patients with PCD and patients with non-PCD–bronchiectasis may display different mechanisms for airway damage, and therefore responses to individual therapies may be quite different.

Conclusions

Despite great scientific advances in bronchiectasis in 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 these clinical overlaps need to be investigated in order to unravel the specific pathophysiology of these conditions. More importantly, both conditions of bronchiectasis overlap with COPD and asthma need a specific definition 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, given that a specific treatment could therefore be indicated, *e.g.* ICS in patients with eosinophilic airway 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 airway diseases are understood only in the 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 in 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 prognoses but unfortunately there is still scarce information available. Moreover, it is unknown whether these different clinical entities share any common pathways in terms of airway inflammation and lung injury or to what extent they can be considered different airway diseases. In particular, it is crucial in bronchiectasis to identify overlap-specific risk factors contributing to increased susceptibility to infection (both acute and chronic). Only large databases and longitudinal studies can answer these crucial questions and identify modifiable prognostic factors. Specific biomarkers, more appropriate imaging or functional techniques could support the follow-up of disease progression and help define the personalised management of these overlap conditions.

Finally, we desperately need to define specific therapeutic tools for each overlap disease, or clinical phenotype, according to the 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 share biological mechanisms that lead to the development of bronchiectasis, but clear differences can be described in terms of the clinical, functional, radiological, microbiological and biological aspects. These differences determine distinct phenotypes, or overlap syndromes, that require targeted interventions [156, 157]. As such, the concept of precision medicine would perfectly fit this field. A precise intervention on treatable traits could lead to optimal management of each condition and improve short- and long-term outcomes [157].

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

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