COPD – Bronchiectasis Overlap Syndrome.

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The overlap between Chronic Obstructive Pulmonary Disease (COPD) and bronchiectasis is a neglected area of research and there are no guidelines for clinical practice. We provide a position statement from the BRONCH-UK consortium, intended to be of interest to both the clinician and researcher. Whilst making recommendations based on expert consensus, one of our aims is to provoke debate. Through discussion of this overlap we also aim to promote research in the area, driving improvements in patient care.

1. Definitions and Diagnosis: why an overlap syndrome and/or co-diagnosis exists

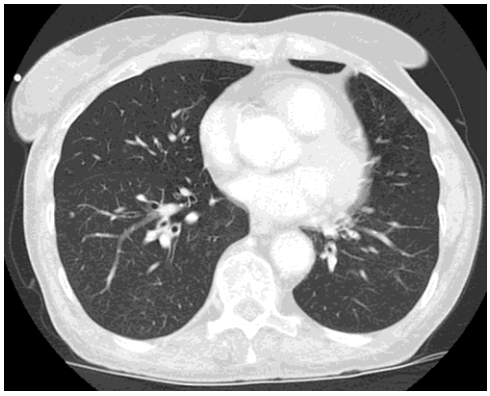
COPD and bronchiectasis share common symptoms of cough with sputum production and susceptibility to recurrent exacerbations driven by new or persistent infection. Patients presenting *de novo* may therefore present a diagnostic challenge.

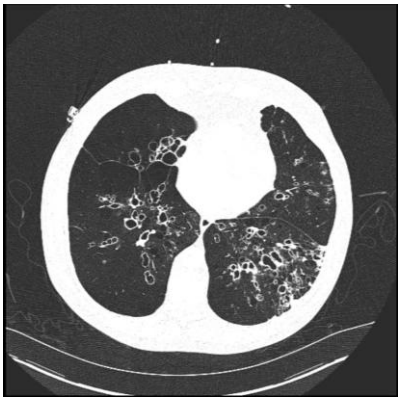
COPD is diagnosed on the basis of poorly reversible airflow obstruction, and is therefore a physiological diagnosis. It is defined [1] when an objective measure of airflow obstruction is associated with an abnormal inflammatory response of the lung to noxious stimuli, with cigarette smoke the most common exposure in the developed world. Operationally this implies that patients with any sufficient exposure and fixed airflow obstruction are labelled as having COPD.

Bronchiectasis is diagnosed in the presence of airway dilatation and airway wall thickening on imaging (usually computed tomography, CT) and is therefore a structural diagnosis. Clinically significant disease is present when imaging abnormalities are associated with symptoms of persistent or recurrent bronchial infection [2]. An increasing number of patients with COPD have a CT scan as part of their diagnosis and follow-up care, with consequent impact on detection of airway wall changes. Airway wall changes in COPD are typically mild and diffuse, whereas those in bronchiectasis may be localised or diffuse depending on the aetiology, and mild or more severe including varicose and/or cystic change (Figure 1).

Physiologic criteria for the diagnosis of COPD, and structural criteria for the diagnosis of bronchiectasis create the possibility for individual patients to fulfil both, resulting conceptually in either co-diagnosis or an overlap syndrome between the two conditions. The prevalence of this overlap will vary depending on the respective prevalence of COPD and bronchiectasis in the population under consideration.

FIGURE 1: Typical airway wall changes in COPD (left) are diffuse, and may be associated with co-existent emphysema. Airway wall changes in primary bronchiectasis (right) may be localised or diffuse, and may be more severe resulting in cystic and/or varicose appearances.





2. Why the overlap between COPD and Bronchiectasis is important.

What is the relevance for patients who fulfil both diagnoses? Establishing the primary diagnosis is important as it has implications for optimal diagnosis and treatment.

Firstly, the range of necessary aetiological investigations differs with resultant resource implication. For example, the low pick up rate for alpha-1 antitrypsin deficiency in bronchiectasis means that testing is not recommended in the aetiological work up for bronchiectasis [2]. In contrast, the GOLD document recommends such testing in early onset and/or severe COPD. Assessment of serum immunoglobulins is mandatory in the assessment of bronchiectasis, but does not currently form part of COPD guidelines, even in patients experiencing recurrent exacerbations. Establishing a primary diagnosis of COPD with secondary changes of bronchiectasis versus primary bronchiectasis with secondary fixed-airflow obstruction can be challenging. In patients who have smoked, a preceding long history of dyspnoea without infective symptoms, the presence of emphysema, and mild, diffuse bronchiectasis all suggest that COPD is the primary problem. A smoking history less than 20pack years makes COPD less likely and, anecdotally, many patients with primary bronchiectasis have never smoked.

Secondly, treatments useful in COPD may not be widely effective in bronchiectasis and *vice versa*. Inhaled corticosteroids provide perhaps the best example of this, widely used in COPD and not recommended for most patients with bronchiectasis [2]. The reasons for this are unclear, but likely reflect, in part, the diverse aetiology underlying bronchiectasis. In contrast, inhaled antibiotics, including anti-*Pseudomonal* agents in appropriate patients [3], are of benefit [4] and appear in current bronchiectasis guidelines [2] but are not used routinely in stable COPD. Bronchiectasis guidelines [2] suggest 14 days of antibiotics for treating bronchiectasis exacerbations but courses in COPD should be considerably shorter. Extrapolating this to COPD-associated bronchiectasis could greatly increase the use of antibiotics at a time when antimicrobial resistance is a major concern. However, as noted below, this group of patients have a poorer prognosis and therefore there remains the need to identify which regimes are most effective.

3. The importance of anatomic bronchiectasis in COPD.

The prevalence of airway wall thickening and dilatation that would fulfil the definition of bronchiectasis increases with increasing spirometric severity of COPD. A key UK study [5] found that 30% of a primary care COPD population had airway wall abnormalities potentially classifiable as bronchiectatic. There is currently much interest in identifying specific 'phenotypes' of COPD: groups of patients with specific characteristics who may respond to a particular therapy, or experience a particular prognosis. Phenotypes may co-exist and it is likely that there is an overlap between airway wall thickening and dilatation on CT suggesting bronchiectasis and the chronic bronchitis phenotype. It is important to recognise that standardisation in reporting of airway wall thickening and dilatation is challenging, and may be different across studies with the resultant risk of over-diagnosis. At present, COPD is not considered a cause of bronchiectasis. However, whilst significant studies with longitudinal data are lacking, the high prevalence of airway wall abnormalities in COPD challenges this assumption. A recent study of 201 COPD patients with airway wall abnormalities typical of bronchiectasis confirmed an association with exacerbations, and was predictive of mortality over 48 months [6]. A further, single centre study demonstrated a near three-fold increased mortality rate, with patients with bronchiectasis and associated COPD having a five year mortality of 55% compared to 20% in those with bronchiectasis without COPD [7]. In comparison, the landmark TORCH Trial in COPD had a 3 year mortality rate of less than 20% [8]. With the increasing clinical use of CT in patients with COPD (assessment for volume reduction, screening for lung cancer, coronary artery calcification assessment and investigation of nodules and haemoptysis, for example), the presence of "bronchiectatic" airway wall changes is increasingly documented and the implications of this need to be established.

4. The importance of fixed airflow obstruction in bronchiectasis.

When examining collections of patients known to clinicians in secondary care, a proportion of patients will exhibit fixed airflow obstruction, and therefore meet the spirometric diagnostic criteria for COPD. However, the prevalence of fixed airflow obstruction in bronchiectasis varies by the population of bronchiectasis patients studied, a problem common to much bronchiectasis research. Airflow obstruction is perhaps best considered one marker of disease severity in bronchiectasis. Known for some time, this has more recently been operationalised with the development of two prognostic scores – BSI [9] and FACED [10] – both of which include FEV_1 as a component in the prognostic models [11] (though FEV_1 may also be reduced in the context of restrictive disease). There is clearly real need to develop new therapies to address the small airway disease common to both conditions that is the most important site of airflow obstruction.

5. Recommendations / Summary.

In summary, COPD and bronchiectasis may co-exist as an overlap syndrome. Two studies suggest the overlap is associated with increased mortality.

We make the following recommendations:

1. It is important to assess whether COPD or bronchiectasis is the primary diagnosis, to guide investigative strategy and treatment (Table 1). In those patients where this is not possible, investigating both conditions may be necessary.

2. In patients with primary bronchiectasis, fixed airflow obstruction is best considered one marker of disease severity, identifying patients with a poorer prognosis. The mechanisms, risk factors and potential management options for these patients are largely unknown demanding more research.

3. The anatomic airway abnormalities of bronchiectasis in patients with primary COPD are best considered a phenotype of the COPD disease spectrum. Further work is needed to define the pathogenesis and clinical consequences of this phenotype, particularly in terms of prognosis and whether the presence of anatomical bronchiectasis should alter the therapeutic approach.

4. For patients with both diagnoses, who therefore have a true overlap syndrome, there is the need to understand more about the condition with specific regard to epidemiology, natural history, and treatment.

TABLE 1: Is COPD or bronchiectasis the primary diagnosis?

	COPD	Bronchiectasis
History of Respiratory Exposure, typically to Tobacco smoke	Necessary*	Not necessary
Fixed Airflow Obstruction	Necessary	Not necessary
Airway Wall Abnormality at CT	Not necessary	Necessary

*: except Alpha-1 antitrypsin deficiency

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