Is bronchiectasis really a disease?

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Despite the heterogeneity in phenotype and response to treatment, bronchiectasis should be defined as a disease, and the large heterogeneity and overlap in pathogenesis, clinical features and response to treatments should be regarded as treatable traits http://bit.ly/2YL02lQ

ABSTRACT   The definition of a disease requires that distinguishing signs and symptoms are present that are common, and that the constellation of signs and symptoms differentiate the condition from other causes. In bronchiectasis, anatomical changes, airways inflammation and airway infection are the distinguishing features that are common to this disease. However, bronchiectasis is a heterogenous disease: signs and symptoms are shared with other airway diseases, there are multiple aetiologies and certain phenotypes of bronchiectasis have distinct clinical and laboratory features that are not common to all people with bronchiectasis. Furthermore, response to therapeutic interventions in clinical trials is not uniform. The concept of bronchiectasis as a treatable trait has been suggested, but this may be too restrictive in view of the heterogeneity of bronchiectasis. It is our opinion that bronchiectasis should be defined as a disease in its own right, but one that shares several pathophysiological features and "treatable traits" with other airway diseases. These traits define the large heterogeneity in the pathogenesis and clinical features and suggest a more targeted approach to therapy.

Introduction

What is a disease? According to the Merriam–Webster dictionary, the definition of disease is "a condition of the living animal […] or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms". However, what counts as a disease may evolve over time. As an example, age-related dementia is an example of a process with dire consequences for the inflicted individuals and their family, but previously dementia was viewed as a normal phenomenon of ageing and was not classified as a disease until 1906 [1].

Development of diagnostic technologies may also change what we classify as disease [2]. "Asthma" has been described for centuries, the term thought to have originated from an ancient Greek word meaning "panting" [3]. Therefore, the term "asthma" was used to describe all causes of breathlessness. With the

development of diagnostic tests that could measure airway calibre, the term was narrowed to the process that causes reversible bronchial constriction. Further development in definitions of bronchial inflammation allowed us to refine and differentiate between different phenotypes of asthma. Thus, improvements in diagnostic technology allow us to define "new" diseases and refine definitions of old ones.

The invention of the stethoscope by Laennec enabled him to describe the clinical features of bronchiectasis for the first time and correlate with anatomical findings [4]. However, bronchiectasis was not frequently acknowledged until the last two decades when it was appreciated that there was a greater prevalence of bronchiectasis and consequently greater attention and research [5, 6]. High-resolution computed tomography (HRCT) scanning allowed detection of bronchiectasis in people with symptoms that may have been previously diagnosed as other diseases based on clinical features (e.g. asthma or chronic bronchitis). Recent advances in phenotyping patients with bronchiectasis (e.g. biomarkers or genetics) may further change the way we classify bronchiectasis.

In this review we will attempt to outline the arguments in favour and against labelling bronchiectasis as a disease, looking at pathogenesis, aetiology, clinical features, patterns of inflammation and infection and efficacy of treatment modalities. Lastly, we will focus on implications of the different approaches to labelling bronchiectasis as a disease or otherwise.

Thesis: bronchiectasis is a disease

Bronchiectasis fulfils the dictionary definition of a disease. It is unquestionably the result of impaired function of the airways and is characterised by distinguishing signs (i.e. radiographic features) [7, 8]. Although there are a number of aetiologies or associated conditions, a common pathophysiological mechanism has been suggested, in which impaired mucociliary clearance and retention of airway phlegm, consequent bacterial infection and inflammation contribute to a destructive process, leading to one another and propelling bronchiectasis [9, 10].

A central feature of most cases of bronchiectasis is airway inflammation. GAGA et al. [11] found increased inflammatory infiltrates in bronchial biopsies performed in patients with bronchiectasis compared with healthy controls. Studies have further characterised inflammatory cells to include lymphocytes (predominantly CD4 positive, with a smaller proportion of CD8 positive), abundant neutrophilic infiltrate and increased presence of interleukin (IL)-8 [11–15]. Elevated neutrophil count has been strongly correlated with impaired lung function, bronchiectasis severity and disease duration [11]. Neutrophil elastase, a serine protease produced by neutrophils and excreted in response to infectious stimuli [16], has been found to increase in quantity during exacerbations of airways disease and decrease after treatment of the exacerbation and with resolution of symptoms. In bronchiectasis due to cystic fibrosis (CF), neutrophil elastase level was significantly correlated with the rate of lung function decline [17]. In different research settings, neutrophil elastase has been proven to contribute to disease severity being associated with an elevated risk of exacerbations, lung function decline and mortality [18].

Another common finding in bronchiectasis is persistent infection of the airways by bacterial pathogens, most notably *Pseudomonas aeruginosa*, *Haemophilus influenza*, *Staphylococcus aureus* and non-tuberculous mycobacteria (NTM) as well as fungi [13, 19–22]. Infection with *P. aeruginosa* is associated with worse outcomes including more frequent exacerbations, worse quality of life and elevated mortality [22–25]. Inflammation is increased in people chronically infected with *P. aeruginosa* and decreased in response to antimicrobial treatment, both short- and long-term [26].

We approach disease as a process that is responsive to therapy targeted towards the pathogenesis or its downstream consequences. Recommended therapies for people with bronchiectasis primarily target the consequences of bronchiectasis, such as airway obstruction and infection [27–29], but not all therapies have equally established evidence of efficacy, nor will all patients benefit from all of these therapies. Airway clearance techniques have been shown to improve mucus expectoration [30–34], measures of airway inflammation [35], lung function [32], quality of life [30, 31, 35] and also to reduce pulmonary exacerbations [30]. Antimicrobial treatment for acute exacerbations is recommended [27–29] with evidence from small studies showing benefit in symptoms (sputum volume and purulence, cough, dyspnoea) [36, 37], lung function [38] and inflammation [26, 36, 37]. Long-term antimicrobial treatment with macrolide antibiotics was found to decrease pulmonary exacerbations and symptoms [39–41]. Studies of long-term inhaled antimicrobials have not shown consistent results but there are reports of success in reduction of exacerbations [42–45]. Incorporating the various aspects of bronchiectasis care into clinical practice results in improved clinical outcomes; it has been shown that in patients under care at bronchiectasis centres, exacerbation frequency is reduced over time [46].

Antithesis: bronchiectasis is not a disease

Fundamentally, the word bronchiectasis means dilation of the bronchi; as such it describes an anatomical abnormality. There are few other examples of anatomical, pathological or radiological terms which are also used to describe diseases. This is because most such abnormalities usually can be caused by multiple diseases or pathological processes. One example in the respiratory field of an anatomical abnormality also used to describe a disease is pulmonary fibrosis. This term might be said to meet the criteria set out in the introduction for diseases, since it has a defined pathophysiology and set of associated symptoms. Nevertheless, we know clearly that pulmonary fibrosis caused by hypersensitivity pneumonitis is a very different disease with a different treatment to usual interstitial pneumonia or sarcoidosis. Thus, pulmonary fibrosis is a common anatomical phenomenon derived from a number of possible pathologies. It may not always be possible to determine the initiating process (*e.g.* drug induced or hypersensitivity) solely on the basis of the radiological morphology, but it is nonetheless important in order to treat correctly.

Similar to pulmonary fibrosis, typical symptoms of bronchiectasis are not exclusive: productive cough may also occur in COPD (chronic bronchitis) without bronchiectasis, and dry cough (which is classically described in pulmonary fibrosis) may be the main complaint in up to 27% of people with bronchiectasis [47]. Auscultatory findings of wheeze and rales are likewise far from specific. Physiologically, bronchiectasis is classically characterised by obstructive air flow limitation. However, in a prospective multicentre study of 187 patients with bronchiectasis, only 41% had obstruction on spirometry, while 58% had a normal spirogram [48]. Another study of 277 patients found an obstructive pattern in 43%, and 28.7% had a restrictive or mixed pattern [49].

Radiological bronchiectasis is not specific or sensitive

The diagnosis of bronchiectasis is based upon the demonstration of airway dilatation on imaging. However, defining this feature as the hallmark of bronchiectasis is problematic for several reasons. First, radiological bronchiectasis is evident in other airway diseases. In asthma, the prevalence of bronchiectasis is highly variable (more prevalent in severe cases) and ranges between 25 and 68% [50–55]. Likewise, there are several studies performing HRCT chest scans that have found a prevalence of bronchiectasis >57% in patients with COPD [50, 56–64].

One of the criteria for the diagnosis of bronchiectasis on HRCT chest scan is that the ratio of the bronchus to an accompanying blood vessel is >1. However, chest CT scans in elderly people without pulmonary symptoms have found increased bronchial diameter and an increase in bronchial wall thickness in 40–60% of healthy elderly subjects [65–68]. Similar findings have been described in people with rheumatoid arthritis (RA) with no pulmonary symptoms [69]. Therefore, mild radiological airway dilatation, or cylindrical bronchiectasis, may be typical of normal ageing and be clinically unimportant.

Radiological features of bronchiectasis are not specific to clinical features of bronchiectasis. As an example, bronchiectasis can be a feature of idiopathic pulmonary fibrosis (IPF), which behaves differently from other cases of bronchiectasis as it is not typically associated with neutrophilic inflammation and is uniformly excluded from the clinical definition of bronchiectasis in clinical practice and in registries [70, 71] and clinical trials.

The finding of airway dilatation on HRCT may not be sensitive for the detection of early airway disease that may eventually lead to overt bronchiectasis. In CF, it has been demonstrated that early structural airway changes are dependent on the scanning protocol, and expiratory CT chest scans may result in a low sensitivity for detection of airway abnormalities [72]. Likewise, in children, protracted bacterial bronchitis (PBB) [73] and chronic suppurative lung disease (CSLD) [74] are clinically similar to bronchiectasis (*e.g.* persistent symptoms, airway neutrophilia and chronic bacterial airway infection) without evidence of bronchiectasis on imaging [75]. There is also evidence of "chronic wet cough" in adults without bronchiectasis [76], which is hypothesised to be the adult equivalent of PBB/CSLD [77]. It may be hypothesised that these two entities represent early stages of bronchiectasis, which may be reversible with treatment [78].

In accordance with the entities of PBB and CSLD, there is no threshold for defining the minimal changes on chest HRCT that are compatible with the definition of bronchiectasis. Likewise, treatment recommendations do not change according to the extent of radiological involvement [27, 28, 79], and it is not recommended to monitor changes in the extent of bronchiectasis on follow-up chest CT scans. Finally, although radiological bronchiectasis is required to make the diagnosis, there is a poor correlation between severity measures of bronchiectasis (*e.g.* symptoms, exacerbations and mortality) and the extent of bronchiectasis on chest HRCT [24, 25]. In conclusion, typical HRCT chest findings are a prerequisite to the diagnosis of bronchiectasis but are neither specific, sensitive, related to disease progression and prognosis, nor to treatment recommendations. These data suggest that bronchial dilatation may be a

consequence of the underlying disease rather than being the disease itself, and may be prevented with early treatment directed at the underlying disease as has been suggested in PBB/CSLD.

Bronchiectasis is heterogeneous and comprised of many different clinical entities

Bronchiectasis has many phenotypes that are distinct from each other [10]. Some of these phenotypes are considered aetiologies (*e.g.* bronchiectasis associated with inflammatory bowel disease or with COPD) while others are a description of distinctive clinical features (*e.g.* "dry bronchiectasis") [47]. One of the best studied but not the most common, is the phenotype of CF-associated bronchiectasis. CF is thought of as a clinical syndrome of single gene disorder resulting in multiorgan involvement, with bronchiectasis as the pulmonary manifestation. Coordinated centre-based CF care developed early on and separately from that of bronchiectasis, and it is probably for historic reasons that CF is excluded from bronchiectasis registries, clinical trials and guidelines [27, 80]. However, in recent years it has been increasingly acknowledged that cystic fibrosis transmembrane regulator (CFTR) dysfunction is increasingly common among people with bronchiectasis [81–86]: There is increased frequency of CF-causing mutations [81, 82] and other CFTR variants [84, 86] than the frequency in the general population, as well as physiological abnormalities that are related to CFTR deficiency in people with bronchiectasis [86, 87]. It is therefore more useful to acknowledge that CFTR dysfunction is contributing to many people with bronchiectasis, rather than to make the simple distinction of CF and non-CF bronchiectasis.

Similar to CF, other phenotypes of bronchiectasis exist that have distinct aetiology, clinical features and therapeutic modalities. Perhaps the best example is primary ciliary dyskinesia (PCD). Like CF, PCD has a distinct genetic aetiology, albeit more complex and not always identified [88]. Like CF, PCD shares airway pathology with bronchiectasis but has distinct clinical features and extrapulmonary involvement (*i.e.* middle ear infections, situs abnormalities, sperm dysmotility in males) [89]. Ongoing clinical trials (*e.g.* inhibition of epithelial sodium channel, ClinicalTrials.gov Identifier: NCT02871778) test therapeutic modalities in people with PCD and may lead to the first registered therapy for this indication. However, PCD is currently considered as one of the aetiologies of bronchiectasis and people with PCD-bronchiectasis are included in bronchiectasis registries and some clinical trials [90]. The convention that CF-bronchiectasis is considered a different entity from bronchiectasis, while PCD-bronchiectasis is not, is therefore methodologically inconsistent. For this reason, use of the term "non-CF bronchiectasis" is now discouraged [91].

Other examples of bronchiectasis with distinct clinical features and specific treatment modalities also exist. These are immune deficiencies, genetic and acquired (haematological malignancies), that may be treated with immunoglobulin replacement therapy, autoimmune-related (such as RA and inflammatory bowel disease (IBD) and allergic bronchopulmonary aspergillosis (ABPA), for which treatment with systemic corticosteroids and anti-IgE antibodies are indicated. Asthma, COPD and chronic rhinosinusitis (CRS) that are frequently causes and/or associated with bronchiectasis [50], have distinct treatment modalities, as summarised in table 1.

Airway inflammation in bronchiectasis may also not be uniform. In the study by DENTE *et al.* [15] most patients with bronchiectasis had elevated sputum neutrophils. However, 20% of patients had more than 3% eosinophils in sputum, with total sputum eosinophil count ranging from 0 to 70%. A subgroup of eosinophilic predominant inflammation was also found in 17.5% of 40 patients in another study [92]. Similarly, in a previous single-centre study of people with bronchiectasis, presence of CRS was associated with elevated peripheral blood eosinophils and IgE [93]. It may be that some people with bronchiectasis have a type 2 inflammation, perhaps associated with asthma, CRS and ABPA, while the majority of people with bronchiectasis have a neutrophilic inflammation. These differences may be important in developing treatments that target inflammation in bronchiectasis.

Chronic infection is common in bronchiectasis, with *P. aeruginosa* being the most common organism isolated [22, 47, 71]. However, presence of chronic infection is not uniform and ranges from 16% to 50% in different series. While infection with *P. aeruginosa* is associated with worse outcomes [24, 25], The impact of *P. aeruginosa* is also heterogeneous in relation to exacerbation frequency [22]. It is hypothesised that the immune response to infection may impact on disease severity [94, 95].

Response to therapeutic interventions is not uniform and not specific

While there are recommended treatments for patients with bronchiectasis, based on published evidence, these treatments are not uniformly successful in all patients with bronchiectasis. The best examples may be treatments that were first indicated for CF, such as rhDNase [96] and inhaled tobramycin [97] which, in bronchiectasis, did not result in successful outcomes. However, in some of the clinical trials, there was evidence of benefit in some patients, with no success in identifying subgroups of patients in whom efficacy is clear. One example is the efficacy of inhaled corticosteroids (ICS) in people with bronchiectasis.

TABLE 1 "Treatable traits" of bronchiectasis

Trait	Main diseases that share the trait	Clinical features	Laboratory/physiological features	Targeted treatment
Chronic infection	Protracted bacterial bronchitis Chronic bronchitis (COPD)	Chronic wet cough	Growth of pathogens in respiratory secretions	Antimicrobials
Ciliary dyskinesia	PCD Secondary ciliary dyskinesia[#]	Young age of symptom onset, chronic otitis media, situs abnormalities, male infertility (asthenospermia), sinusitis	Low nasal NO, electron microscopic abnormalities, abnormal ciliary beating pattern	Inhaled saline, airway clearance, ongoing trial of ENaC inhibition
CFTR dysfunction/ deficiency	CF CFTR-related disorder Secondary CFTR dysfunction[#]	Young age of symptom onset, pancreatitis, malnutrition, bowel obstruction, male infertility (azoospermia), sinusitis	Elevated sweat chloride, characteristic electrophysiological abnormalities, CFTR mutations on two alleles	CFTR modulators
Immune deficiency	Primary immune deficiencies	Young age of symptom onset, infection in extrapulmonary sites	Immunoglobulin deficiencies, impaired tests of immune function	IVIG
	Secondary immune deficiencies	Haematological malignancies		
Systemic inflammation	Rheumatoid arthritis	Symmetric arthritis, morning stiffness	Rheumatoid factor	DMARDs, CS, anti-TNF-α
	IBD	Bloody diarrhoea, weight loss, GI ulceration	Endoscopic appearance and histology	Aminosalicylates, CS, anti-TNF-α
Eosinophilic inflammation	Asthma	Seasonality	Airway reversibility	ICS, bronchodilators, anti-IgE, anti-IL-5
	CRS	Chronic nasal discharge, loss of smell, facial pain	Sinus inflammation on endoscopy, sinus CT	
	ABPA	Wheeze, mucus plugs	Elevated IgE, *Aspergillus* spp. sensitisation	
Gastro-oesophageal reflux	GORD	Symptoms of heartburn and reflux	Endoscopic, motility and imaging studies	Behavioural measures, proton-pump inhibitors, surgery

Examples of features of bronchiectasis that define a subgroup of patients. These may be viewed as "treatable traits" and some are shared with other disease entities. CFTR: cystic fibrosis transmembrane regulator; PCD: primary ciliary dyskinesia; NO: nitric oxide; ENaC: epithelial sodium channel; CF: cystic fibrosis; IVIG: intravenous immunoglobulins; DMARDs: disease modifying antirheumatic drugs; CS: corticosteroids; TNF: tumour necrosis factor; IBD: inflammatory bowel disease; GI: gastrointestinal; ICS: inhaled corticosteroids; Ig: immunoglobulin; IL: interleukin; CRS: chronic rhinosinusitis; CT: computed tomography; ABPA: allergic bronchopulmonary aspergillosis; GORD: gastro-oesophageal reflux disorder. [#]: may be induced by smoking.

Single-centre studies demonstrated significant reductions in sputum production and improvement in symptoms in patients with bronchiectasis [98, 99]. However, later studies did not show a similar benefit although cough was significantly improved [100]. Currently, treatment with ICS is not recommended in people with bronchiectasis, unless indicated for concomitant asthma or COPD [27]. It remains to be seen whether future studies will be successful in defining subgroups of patients, perhaps according to patterns of inflammation, which will be responsive to previously tested modalities, such as ICS, inhaled antibiotics and rhDNase.

Therapeutic modalities with established efficacy in bronchiectasis are also far from specific and beneficial in other airway diseases. Macrolides have proven efficacy in reducing exacerbations in CF [101], but also in diffuse panbronchiolitis [102, 103], bronchiolitis obliterans in lung transplant recipients [104–106], COPD [107–109], CRS [110] and, recently, asthma [111]. Airway clearance and inhaled mucolytic agents, such as hypertonic saline, are the first-line treatment for CF [112]. Rehabilitation has established benefits in COPD care [113], only later to be utilised in bronchiectasis.

Is bronchiectasis a "treatable trait"?
The concept of "treatable traits" in airway diseases was recently introduced [114]. It was suggested that, in the age of precision medicine, a pragmatic, therapy-focused approach to airway disorders would be more successful in treatment than classifying diseases and treating accordingly. Focusing on asthma and COPD, classifying people into "diseases" may lead to suboptimal management because diseases with different

endotypes require different therapeutic strategies. The classical approach limits our investigation of the causes of morbidity of people whose symptoms do not meet the definition of one airway disease. This may result in limited development of drugs that target one endotype and not another. Lastly, this approach may also limit the generalisability of clinical trials, because many patients with a "disease" targeted in clinical trials may have features of another "disease" and therefore are excluded from those trials, obvious examples being the exclusion of people with airway reversibility from COPD trials and smokers from asthma trials. The list of traits of airway diseases that was included in that paper contained, among others, emphysema, eosinophilic inflammation and bronchiectasis.

Emphysema is considered to be a trait of people with the "classic" definition of COPD. Similar to bronchiectasis, radiological emphysema may be asymptomatic or be associated with severe symptoms (e.g. exercise intolerance). It is therefore not considered a disease by itself, but a clinical feature, or trait, of people with COPD, especially smokers and, in the presence of α_1-antitrypsin deficiency. Lung volume reduction is a therapeutic option that targets emphysema, making the trait a treatable one [115].

Bronchiectasis was suggested to be one of the treatable traits of airways diseases [114]. However, the diversity of bronchiectasis would make it very difficult to narrow into a treatable trait as the treatable aspect suggests there is a narrow indicated treatment such as inhaled corticosteroids for the treatable trait of eosinophilic inflammation. Rather, we suggest that bronchiectasis be viewed as a disease that is heterogeneous and shares treatable traits with other diseases. Examples of treatable traits of bronchiectasis may be airway infection (targeted by antimicrobials), failure of mucociliary clearance (treatable with airway clearance and pharmacological adjuncts) and CFTR dysfunction (treatment with CFTR modulators). Table 1 shows several examples of such treatable traits that are shared by subsets of people with bronchiectasis and other airway and systemic diseases. Determining an aetiology or a treatable trait has important implications for future care since identification of the underlying abnormality, which may be inflammatory, ciliary or epithelial in origin, and early treatment may prevent the development of bronchiectasis.

The treatable traits model is powerful specifically because it does not require a clinician to identify a disease or to decide which disease is predominant in a specific circumstance. If your patient has airway infection and frequent exacerbations, they may benefit from antimicrobial and anti-inflammatory treatment with a macrolide regardless of whether the primary disease label is bronchiectasis, COPD or asthma. Likewise, if the patient has exercise limitation and deconditioning, they are likely to benefit from pulmonary rehabilitation regardless of the underlying disease label. Thus, moving from thinking of airway diseases as labels and instead as complex systems composed of multiple traits may lead to more holistic treatment.

Does it really matter?
AGUSTI et al. [114] suggest that the pulmonology community move away from "Oslerian" diagnoses towards treatable traits definitions, but this approach does have implications to be considered. For health authorities, labelling patients with distinct diagnoses allows planning and distributing health services, drug and treatment registration, and more. For patients, naming their symptoms as a diagnosis may be reassuring, apart from the hope of improving with treatment [116]. A repeated complaint from our patients with bronchiectasis is that their condition was misdiagnosed and neglected for decades. Moving away from labelling bronchiectasis as a disease may wipe away the important achievements of bronchiectasis research and organisation of the past years. In asthma and COPD, heterogeneity and the importance of phenotyping is increasingly recognised. However, the medical community has not moved away from the definition of these diagnoses, and international guidelines on diagnosis and management are still available and regularly updated [113, 117], while important advancement in "precision medicine" directed towards specific phenotypes continue [118, 119]. The same should be the case for bronchiectasis: maintaining the "disease" label while acknowledging its limitations, the heterogeneity of the disease and the importance of identifying treatable traits to appropriately target new therapies.

Conclusion
Bronchiectasis is defined by distinguishing radiological and clinical features. The last decade has brought significant advancement in the understanding of bronchiectasis and improvement of treatment. However, difficulties in establishing therapeutic benefits have highlighted the great heterogeneity in bronchiectasis, and raise the question of appropriateness of regarding bronchiectasis as a single clinical entity. It is our opinion that, similarly to asthma and COPD, bronchiectasis should be defined as a disease, but that the large heterogeneity and overlap in pathogenesis, clinical features and response to treatments be acknowledged.

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