Treatable traits in bronchiectasis

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The diagnostic label "bronchiectasis" describes the existence of localised and permanent airway dilation, but when used to describe a disease it includes a heterogeneous group of disorders that differ significantly in terms of aetiological, clinical, radiological, functional and microbial features [1]. Using cluster analysis, some previous studies have attempted to identify distinct "clinical phenotypes" in patients with bronchiectasis [2–4] (defined as "a single or combination of disease attributes that describe differences between patients that are related to clinically meaningful outcomes" [5]). By and large, however, these studies did not consider the underlying biology or response to therapy (*i.e.* the underlying endotype(s) [6]). Potential endotypes in bronchiectasis include immunodeficiency, ciliary dyskinesia, infection (with typical bacteria and non-tuberculous mycobacteria (NTM)), hypersensitivity to fungi and autoimmunity. Importantly, all of them can potentially become therapeutic targets [7].

The main treatment goals in bronchiectasis are to reduce symptoms, prevent exacerbations and lung function decline and, ultimately, improve survival. Unfortunately, most currently available therapeutic options have shown only a modest impact on disease outcomes in randomised clinical trials [8, 9]. For instance, inhaled antibiotic treatments have, so far, produced only modest benefits in terms of reduced exacerbations or improved quality of life, suggesting that endotypes other than airway "infection" are likely to play a relevant pathogenic role [10–12]. Likewise, co-existing airways diseases are common in patients with bronchiectasis and, in fact, up to 50% of these patients have a diagnosis of co-existing asthma or chronic obstructive pulmonary disease (COPD) [13, 14]. All in all, the complexity of bronchiectasis is poorly adapted to the "one size fits all" approach of current clinical guidelines. The co-existence in the same patient of different endotypes, clinical phenotypes and exposures requires a more precise approach to both assessment and therapy.

The concept of "treatable traits" was originally proposed in 2016 by Agusti *et al.* [15] in the *European Respiratory Journal* as a way toward precision medicine of airway diseases. These authors argued that the current airways disease diagnostic labels are imprecise, often overlap and lead to empirical therapy. They proposed that a biomarker-directed approach, based on the recognition of clinical phenotype and endotypes, can help to personalised treatment options which, hopefully, may result in better clinical outcomes. In the original manuscript on treatable traits, bronchiectasis was considered as a potential trait in patients with a diagnostic label of asthma or COPD. Here, we leverage from the treatable traits concept [15] and suggest that patients with bronchiectasis, with or without co-existing COPD and asthma, represent a heterogeneous group of patients who also present multiple treatable traits, many of which go

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TABLE 1 Proposed treatable traits of bronchiectasis separated into aetiological, pulmonary, non-pulmonary and environment/lifestyle categories

	Diagnostic criteria	Treatment	Expected benefits of treatment
Pulmonary			
Infection[#]	Clinical features Sputum characteristics Inflammatory markers Sputum culture	Airway clearance [33, 34] Prompt treatment of exacerbations Long term oral or inhaled antibiotics	Reduce exacerbations Improve quality of life
Chronic *Pseudomonas* infection	Two or more culture isolates at least 3 months apart in 1 year [35]	Long term inhaled antibiotics Long term macrolides Airway clearance Eradication at first isolation [8]	Reduce exacerbations Improve quality of life [36] Slow lung function decline Prevent chronic infection [37]
Mucus hypersecretion	Volume Colour of sputum	Airway clearance Airway adjunct devices [27, 28] Mucoactive drugs Anti-inflammatories	Reduce sputum volume Reduce viscosity/increase ease of expectoration
Mucus plugging	Clinical features CT scan	Airway clearance Mucoactive drugs Nebulised saline Anti-inflammatories	Reduce sputum volume Reduce viscosity/increase ease of expectoration
Airflow obstruction	$FEV_1/FVC<LLN$ Fixed ratio spirometry GLI equations	Bronchodilators Smoking cessation Exercise	Improved exercise capacity and functional status [8]
Asthma	Bronchodilator reversibility Peak expiratory flow variability Elevated sputum or blood eosinophils	ICS Systemic corticosteroids Bronchodilator Leukotriene receptor antagonists Monoclonal antibody anti-IL-5, anti-IgE [38]	Reduce exacerbations
Eosinophilia	Elevated sputum or blood eosinophils Exclude other causes of eosinophilia	ICS Systemic corticosteroids Treatment for underlying cause	Improve QoL and treatment response
NTM infection[¶]	Positive culture and clinical/radiological findings	Long term antibiotic [39]	Improve QoL and achieve remission [40, 41]
Aspergillus sensitisation	Elevated specific IgE/prick test positive	ICS Systemic corticosteroids Antifungals	Reduce exacerbations Reduce sputum production Improved QoL [21]
Bronchial hyperreactivity	Challenge tests	ICS	Reduce exacerbations
Cough hypersensitivity	Clinical features Search other potential extrapulmonary causes Capsaicin cough challenge	Antitussive Chest physiotherapy	Improve QoL
Respiratory insufficiency	P_{aO_2} <55 mmHg P_{aCO_2} >45 mmHg	Long term oxygen and/or noninvasive ventilation	Improve quality of life Improve survival
Aetiological			
Primary immunodeficiencies	Serum immunoglobulins levels Specific antibody levels	Reference to immunology specialist Immunoglobulin replacement	Improve outcome Improve QoL Prevent lung damage
Cystic fibrosis	Clinical features Sweat chloride testing, CFTR genetic analysis and/or CFTR physiological testing	Reference to cystic fibrosis clinic CFTR modulators DNAse	Improve outcome Improve QoL Prevent lung damage
Primary ciliary dyskinesia	Clinical features[+] Nasal NO assay Electron microscopy ciliary structure analysis or video recording ciliary function analysis Genetic testing [42, 43]	Genetic counselling Intensive airway clearance Management of upper airway symptoms	Improve outcome Improve QoL Prevent lung damage
ABPA[¶]	Raised specific IgE and/or positive prick skin test to fungi, raised total IgE Other: eosinophilia, radiological features, raised specific IgG/precipitating antibodies against fungi [8]	Systemic corticosteroids and/or antifungals Monoclonal antibody anti-IgE ICS	Improve outcome Improve QoL Prevent lung damage
CTD	Clinical features Serum antibodies	Reference to rheumatologist Immunosuppressors	Improve outcome Improve QoL Prevent lung damage

Continued

TABLE 1 Continued

	Diagnostic criteria	Treatment	Expected benefits of treatment
IBD	Clinical features Serological markers Anatomopathological findings on gut biopsy	Reference to gastroenterologist Immunosuppressors Surgery	Improve outcome Improve QoL Prevent lung damage
Extrapulmonary (comorbidities)			
Depression/anxiety	Questionnaires Psychologist/liaison Psychiatrist assessment	Anxiety management Breathing retraining Cognitive behavioural therapy Pharmacotherapy Support groups	Improve QoL
Obesity/underweight	Body mass index	Nutritional evaluation Regular physical activity	Improve QoL and outcome
GORD	Clinical features Gastric endoscopy pH monitoring	Proton pump inhibitor H2-antagonist Surgery (fundoplication)	Improve QoL
Cardiovascular disease	Clinical features Electrocardiogram Echocardiogram BNP Stress testing	ACE inhibitors Diuretics β-blockers Revascularisation Reference to cardiologist	Improve QoL and outcome
Rhinosinusitis	Clinical features Imaging	Nasal steroids Leukotriene receptor antagonists Antihistamines Immunotherapy Surgery	Improve QoL
Iron deficiency anaemia	Full blood count Reticulocyte count Serum iron tests Exclude other causes	Oral iron supplements Treatment of underlying cause	Improve QoL and exercise capacity
Environment and lifestyle			
Smoking	Patient reported Exhaled carbon monoxide	Tobacco cessation support Nicotine replacement Antidepressants	Improve QoL, lung function, exercise capacity, response to treatment
Lack of exercise/ sedentarism	Cardiopulmonary exercise testing 6-min walk test	Exercise regularly Pulmonary rehabilitation Prescribed exercise programmes	Improve QoL and outcome
Adherence	Prescription refill rate Patient feedback	Education Written instructions Self-management	Improve outcome
Exposure to air pollution	PM_{10} and NO_2 concentrations	Reduce exposure	Reduce exacerbations [44]

Some of the most common traits observed in clinical studies have been listed, but this list is not comprehensive. A different set of treatable traits may be applicable to children with bronchiectasis to include issues of growth and development. CT: computed tomography; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; GLI: Global Lung Function Initiative; ICS: inhaled corticosteroids; IL: interleukin; QoL: quality of life; NTM: nontuberculous mycobacteria; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; CFTR: cystic fibrosis transmembrane conductance regulator; ABPA: allergic bronchopulmonary aspergillosis; CTD: connective tissue disease; IBD: inflammatory bowel disease; GORD: gastro-oesophageal reflux disease; BNP: brain natriuretic peptide; ACE: angiotensin converting enzyme; PM_{10}: particulate matter with a diameter smaller than 10 μm. #: the presence of airway infection itself may not be a treatable trait as such since better measures are required to differentiate infection from "colonisation" where the trait is not contributing directly to disease outcome. Additional measures such as bacterial load or microbiota characterisation may be needed to fully operationalise this trait. ¶: could be aetiological or complication of disease. +: recurrent upper and lower tract infections; recurrent otitis in childhood; infertility; laterality disorders.

unrecognised (hence untreated) in clinical practice [16]. We venture that the application of the treatable traits approach to patients with bronchiectasis may, hopefully, contribute to a more personalised and precise management of these patients and, eventually, to improved clinical outcomes.

The treatable traits approach is attractive in bronchiectasis because it takes a "label free" approach to management. When faced with patients with "COPD–bronchiectasis overlap (BCO)" or "asthma–bronchiectasis overlap (ABO)", or patients with features of all three diseases (ABCO), physicians have been previously asked to consider which is the "predominant disorder" [10, 11, 17–20]. We argue here that this approach is flawed because the concept of overlap syndromes itself is flawed. COPD and asthma are complex and heterogeneous entities, as bronchiectasis is. Clarity is not created by generating another poorly defined clinical entity (*e.g.* ACO, BCO, ABO or ABCO) [13, 17, 18]. An approach that is

more user-friendly in terms of the underlying biology is to overlook diagnostic labels and focus instead on the pathophysiology (*i.e.* endotypes) and clinical phenotypes present in any given patient. This idea is the core of the treatable traits concept. For instance, the treatable traits concept applied to bronchiectasis should recognise that airway infection is only one of many treatable traits in a given patient and, therefore, allows us to understand why antibiotic treatment may not improve outcomes in an individual in whom symptoms or exacerbations are driven by a different treatable trait (*e.g.* upper airway disease, eosinophilia, fungal allergy or comorbidities) [21–24]. This strategy may also help in understanding why randomised clinical trials have shown inconsistent results despite similar design and well-defined cohorts. For instance, patients enrolled in the RESPIRE trials of inhaled dry powder ciprofloxacin had a history of two or more prior exacerbations and positive sputum cultures for respiratory bacteria. Despite apparently enriching for a "treatable trait" of airway infection, four trial arms provided inconsistent results [10–12]; similar inconsistency was seen in the AIRBX studies of aztreonam where two replicate trials with similar subjects showed an improvement in quality of life in one study and not in the other [25]. Likewise, inhaled dry powder mannitol failed to reduce frequency of exacerbations, despite the fact that it modestly improved quality of life [26]. The overall effect sizes in terms of reduced exacerbations or improved quality of life have been modest in bronchiectasis trials in general [10, 11, 25–28]. The presence of multiple competing

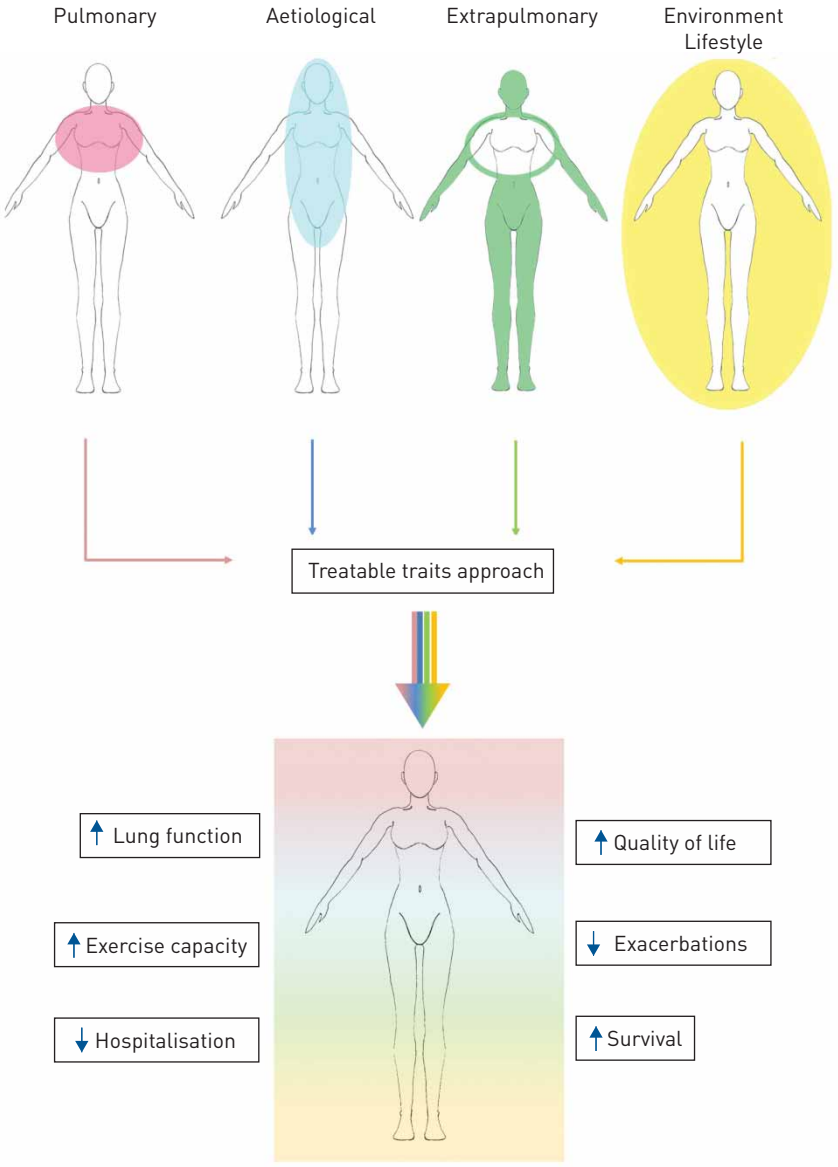

FIGURE 1 Using the treatable traits concept to improve treatment outcomes in bronchiectasis. Recognition and treatment of multiple pulmonary, aetiological, extrapulmonary and environmental/lifestyle associated traits should lead to more holistic treatment and a greater impact on relevant clinical outcomes.

"treatable traits" within the population studied may contribute to explaining why treating a single trait (such as bronchial infection or airway dehydration) achieves only a modest reduction in exacerbations or improvement in symptoms.

The recently published European Respiratory Society (ERS) guidelines for the management of bronchiectasis advocate a number of treatments, including antibiotics, bronchodilators, pulmonary rehabilitation and chest physiotherapy [8]. While some guidance is provided on the optimal populations to benefit (*e.g.* based on prior exacerbation history), patient phenotyping or endotyping is beyond the scope of such a document. Likewise, the guideline cannot address treatable comorbidities, environmental, lifestyle and psychological factors, which can also impact on patient outcomes [2, 29–32]. Providing holistic care for patients with bronchiectasis requires taking these factors into consideration as well. Thus, recognising the limitations of existing approaches, we have applied the treatable traits model proposed by Agusti *et al.* [15] to bronchiectasis. Agusti *et al.* [15] divided potential treatable traits of airways disease into three broad categories (pulmonary, extrapulmonary, and behaviour and lifestyle treatable traits). We think that these same categories apply to bronchiectasis but we propose to add a fourth category for bronchiectasis that includes "aetiological" treatable traits to emphasise the importance of identifying those traits which directly lead to the development of bronchiectasis such as NTM infection, allergic bronchopulmonary aspergillosis and immunodeficiency. Table 1 shows a list of proposed treatable traits, diagnostic criteria, suggested therapies and expected benefits in patients with bronchiectasis. Crucially, this hypothesis should be prospectively tested or, alternatively, analysed retrospectively in randomised clinical trial datasets if pharmaceutical companies are willing to share their data.

In summary, we propose here that the treatable traits approach can be a useful strategy to help clinicians consider the many different aspects that must be addressed for the appropriate clinical management of patients with bronchiectasis. Focusing on a multimodality approach to treatment is likely to result in better clinical outcomes (figure 1) but this should ideally be tested in prospective studies. Identifying the frequency and clinical impact of individual treatable traits in bronchiectasis, as well as determining the best way to address them, will be important in developing this concept further. As suggested in the conclusions of a recent ERS research seminar, in order to prove that the treatable traits strategy is feasible, efficacious and safe in clinical practice, we need to formally test this hypothesis using the novel platform of adaptive trials design [45].

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