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Bronchiectasis : New therapies and new perspectives

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Summary

The recently published European Guidelines for the Management of Bronchiectasis in adults highlight the limited treatment options available for these patients. There remain no therapies licensed by regulatory agencies worldwide and most therapies used in clinical practice have very limited evidence. There is an urgent need to develop new therapies.

Using a systematic review of the literature and clinical trials registries we identified therapies in early to late clinical development for bronchiectasis in adults. This article presents a discussion of the mechanisms and potential role of emerging therapies, including drugs targeting airway and systematic inflammation, mucociliary clearance and epithelial dysfunction.

To ensure these therapies achieve success in randomized clinical trials and therefore reach patients, we propose a re-evaluation of our current approach to bronchiectasis. Although our understanding of the pathophysiology of bronchiectasis is at an early stage, we argue that bronchiectasis is a heterogeneous disease with multiple different biological mechanisms driving disease progression (endotypes) and therefore the “treatable traits” concept of asthma and COPD could be applied to bronchiectasis with future trials targeted at specific subgroups most likely to benefit.

Key Points Panel

1-**In the recent European Bronchiectasis Guidelines, no pharmacotherapy was supported by strong clinical evidence**

2-Multiple recent trials in bronchiectasis have focussed on antibiotic treatment and have failed to reach their primary end-points, suggesting a need to re-evaluate how we use and test therapies in bronchiectasis patients.

3-New therapeutic development in bronchiectasis is focussed an modulating inflammatory processes, including targeting neutrophil, macrophage, T-cell and epithelial function to reverse the underlying disease processes.

4- Bronchiectasis is a heterogeneous disease incorporating multiple different aetiologies, with different radiological, microbiological, inflammatory and physiological subgroups, referred to as phenotypes and endotypes

5-We propose that a "one size fits all" approach to clinical trials and clinical practice in bronchiectasis is unlikely to be successful. Instead, we suggest that the "treatable traits" concept of airways disease could be applied to bronchiectasis to improve therapeutic targeting both in clinical trials and in clinical practice.

Introduction

"This is the age of bronchiectasis".[1] The prevalence of bronchiectasis in the UK increased by 40% between 2004 and 2014 with similar increases observed worldwide.[2] The increasing recognition of the disease is multifactorial including a greater use of CT scanning, greater physician awareness and the recognised overlap between bronchiectasis, asthma and COPD .[3] The increasing burden of the disease on the healthcare system has led to a surge in clinical research, new randomized trials and a global growth in specialist services.[4-10]

Great progress has been achieved and the profile of bronchiectasis within respiratory medicine has never been higher. In September 2017, the first European Guidelines for adult bronchiectasis were published .[4] These guidelines represent the first international standards of care for the disease that follow a number of national guidelines produced in the past decade.[4,5] The publication of these guidelines while an important milestone, illustrate how far we remain to travel to deliver effective therapies to patients.
Of the key treatment recommendations only 1 was supported by high quality evidence: pulmonary rehabilitation.[4] Most recommendations were conditional and based on low or very low quality of evidence (table 1).[4]

There remains no therapy licensed by regulatory authorities worldwide for the treatment of bronchiectasis despite a large number of phase 3 randomized clinical trials. This contrasts with other conditions, notably idiopathic pulmonary fibrosis which have experienced a similar renaissance but where positive phase 3 trials have led to the licensing of new drugs and a positive impact on patients outcomes.[11] The repeated failure of trials in bronchiectasis to give positive outcomes necessitates a re-evaluation of our approach[10,11-15]

In this review, we outline novel approaches to the management of bronchiectasis in adults aiming to take us beyond antibiotics and beyond the recommended therapies in recent guidelines.[4] Furthermore, we propose that recent randomized trials have struggled to show clinical benefits because of the unresolved heterogeneity of bronchiectasis, and that a more logical, stratified approach to therapy will be required going forward.[16] In this light, we offer newer perspectives on strategies to achieve patient stratification that in future, will likely make the disease more amenable to personalised care.

Search strategy and selection criteria

The authors performed a review using PUBMED of all manuscripts published using the keyword "bronchiectasis" since January 2010 to September 2017. As the objective of the review was to identify novel treatment approaches entering clinical trials for adults, the authors searched the international clinical trial registries ISCRTN and clinicaltrials.gov using the search term "bronchiectasis". Randomized clinical trials were selected for discussion based on relevance. The clinical trial registry search identified 172 current randomized controlled trials in bronchiectasis or where bronchiectasis is mentioned as a target indication with 55 actively enrolling. Below we review potential therapeutic approaches to bronchiectasis in early to late clinical development.

Recent randomized clinical trials

The majority of late phase randomized clinical trials to be conducted in bronchiectasis have involved attempts to translate therapies licensed in cystic fibrosis (CF). The first example where this failed was a 1998 trial of recombinant DNAse which showed an increased frequency of exacerbations (relative risk 1.35 95%CI 1.01-1.79), and increased adverse events in the DNAse treated patients.[15] Recent trials have confirmed the view that "CF drugs" cannot easily be translated for bronchiectasis.[10,12,13] Inhaled dry

powder mannitol was tested in a trial of 461 patients with bronchiectasis. The study failed to reach its primary end-point of frequency of exacerbations (rate ratio 0.92,p=0.3) although improvements for secondary end-points of time to the first exacerbation and health related quality of life were seen.[10] The development of inhaled antibiotics has dominated the clinical trial scene in bronchiectasis in recent years with mixed results. Small studies of tobramycin and gentamicin showed positive results but were complicated by relatively high (10-40%) rates of bronchospasm, and to date, these drugs have not been tested in large studies.[17,18] Among larger phase 3 trials, Haworth *et al* recruited 144 patients with chronic *P. aeruginosa* infection and randomized patients to nebulised colistin or placebo.[12] The study narrowly failed to meet its primary end-point of time to the first exacerbation (difference colistin vs placebo of 54 days; p=0.11). Among secondary end-points, a large improvement in quality of life using the SGRQ was noted (mean difference −10.5 points; p=0.006).[12] This study most likely failed to meet its primary end-point due to slow recruitment leading to premature termination of the trial.[12] Aztreonam is another inhaled antibiotic licensed for treatment in CF. Two recent phase III trials in bronchiectasis randomised 266 (AIR-BX1) and 274 (AIR-BX2) patients to aztreonam 75mg three times daily or placebo over the course of two 28-day treatment cycles (with 28-days off treatment between cycles).[13] The primary outcome was the newly developed Quality of Life Bronchiectasis (QoL-B) questionnaire.[13] The trial found a significant change in the QOL-B respiratory symptom score in AIR-BX2 but not in AIR-BX1. Treatment related adverse effects and their associated discontinuations were increased in the Aztreonam treated patients.[13] Reasons for the failure of this study to meets its end-point has been the subject of speculation with likely explanations including the highly heterogeneous study population with many patients having no history of exacerbations and relatively mild disease.[13] The characteristics of included patients included high rates of pulmonary non-tuberculous mycobacterial disease and COPD. Nadig and Flume compared the characteristics of included patients in this study to their own population of severe patients with

bronchiectasis treated with inhaled antibiotics and identified little correlation, suggesting that the trial included a skewed population not representative of 'real-life' clinical practice.[19]

Most recently two large programmes developing different inhaled ciprofloxacin formulations have reported.[20,21] At the time of writing neither study has been reported fully, but published abstracts show that liposomal ciprofloxacin achieved its primary end-point (time to the first exacerbation) in one international RCT (ORBIT 4) for patients with *Pseudomonas aeruginosa* infection and a history of at least 2 exacerbations - HR 0.72 95% CI 0.53-0.97,p=0.03, but failed to achieve the primary end point in the replicate ORBIT 3 trial, HR 0.99 95% CI 0.71-1.38,p=0.97.[20] Pooled data from the total 582 patients showed a significant reduction in time to first exacerbation requiring antibiotics, HR 0.74 95% CI 0.59-0.94,p=0.01 and also a significant reduction in the frequency of exacerbations, relative risk 0.73 95% CI 0.60-0.88,p=0.001.[20]

Dry powder ciprofloxacin was tested in 2 x 2 arm trials, each utilising a 14-day on/off and a 28 day on/off regimen. The RESPIRE 1 study included 416 patients and found that the 14-day on/off regimen prolonged time to first exacerbation, HR 0.53 97.5% CI (0.36-0.80,p=0.0005) and also frequency of exacerbations, incidence rate ratio 0.61 97.5% CI (0.40-0.91,p=0.006).[21] The 28-day on/off regimen had no significant benefit in either end-point. The RESPIRE 2 studies enrolled 521 patients and failed to show a statistically significant improvement in time to first exacerbation or frequency of exacerbations in either arm. RESPIRE 2 was conducted primarily in Asia and Eastern Europe, and found a very low rate of exacerbations (approximately 0.6 per patient/year) despite enriching for patients with chronic bacterial infection and at least 2 exacerbations in the prior year.[21]

Therefore, while many therapies, including antibiotics, mucoactive drugs and others have shown trends toward benefit, none have unequivocally demonstrated improvement in clinical outcomes. Even where improvements of 20-40% in exacerbation frequency are demonstrated, these represent only a modest improvement in outcomes for a disease which often has a devastating effect on quality of life.

The one notable success in bronchiectasis therapy in the past 5 years has been macrolides. 3 trials of azithromycin (2 in adults and 1 in children) and 1 trial of erythromycin showed a significant reduction in the frequency of exacerbations of approximately 50% compared to placebo.[22-25] Nevertheless, these trials were relatively small with the largest including 71 patients treated with azithromycin vs 70 patients receiving placebo.[22-25] Their success in reaching their primary endpoints may relate to the inclusion of patients from a small number of centres in a single region, allowing more homogeneous populations to be included. The lack of large scale trials and the associated risk of side effects and antibiotic resistance explains the conditional recommendation for their use in the ERS guidelines.[4]

New treatments approaches are clearly necessary and, importantly, new ways of performing clinical trials should be considered to overcome the persistent difficulty in achieving positive results. Future studies need to better address patient classification, stratification and our understanding of disease mechanisms. This will, in turn, influence inclusion criteria for clinical trials which to clearly need to be aiming to deliver the 'right treatment to the right patient' rather than the status quo of assessing treatments across a large heterogeneous patient group. The optimal trial endpoints still need to be defined.[26] The frequency of exacerbations is the most robust and clinically important, but the responsiveness and validity of the QOL-B is still to be established. FEV1 is a responsive endpoint in CF but does not change at exacerbation or during therapy in bronchiectasis.[26] There is a need to identify better surrogate endpoints specifically for bronchiectasis.

Novel treatment approaches

The treatment of CF is being transformed by the availability of therapies that target the basic defect.[28] A challenge in bronchiectasis not due to CF is the lack of a basic understanding of why patients develop disease. At present, a therapy targeting the basic defect is only possible in cases with a clearly defined reversible cause such as immunodeficiency, allergic bronchopulmonary aspergillosis or non-tuberculous mycobacterial disease.[28] For most however, no identifiable cause is found.[4] While the concept of preventing bronchiectasis in patients with persistent bacterial bronchitis in childhood has gained acceptance in children, the equivalent concept has not yet been accepted in adults.[29]

New therapeutic development is therefore centred around three components of the "vicious cycle", namely targeting bacterial infection (as discussed above), neutrophilic inflammation and mucociliary clearance. A summary of non-antibiotic therapies in development for bronchiectasis are shown in figure 1. Current randomized controlled trials of non-antibiotic drug therapies are summarised in table 2.

Targeting the neutrophil

Neutrophils are the dominant airway inflammatory cell in the majority of bronchiectasis patients.[30] Patients show elevated numbers of neutrophils and other inflammatory cells compared to healthy controls and consequently show elevated levels of neutrophil derived products such as neutrophil elastase (NE), myeloperoxidase, matrix metalloproteinases, cathepsins, antimicrobial peptides (such as LL-37) and neutrophil derived DNA.[30-32] The limited available studies suggest that bronchiectasis patients neutrophils are essentially normal prior to arriving in the airway but that changes occur in the airway environment that promote neutrophil dysfunction and a failure of bacterial clearance.[33,34] This is unlikely to be true in all patients, as neutrophil defects have been identified in patients with CF , including abnormal degranulation and delayed neutrophil apoptosis, both of which can be reversed by CFTR correctors.[35,36] Abnormal neutrophil chemotaxis is also shown in systematic neutrophils from COPD

patients.[37] Further study is required to delineate similar defects in neutrophils from bronchiectasis patients. Airway neutrophil dysfunction in bronchiectasis may result from a combination of host derived mediators, bacterial virulence factors, and changes induced by "frustrated" attempts to clear biofilm shielded bacteria. Studies from the 1980's and 90's suggested a key role for neutrophil elastase in mediating neutrophil dysfunction, through cleavage of multiple cell surface receptors such as CR1, FCYRIIIb, CXCR1 and others involved in phagocytosis.[30] NE is thought to slow ciliary beat frequency, promote mucus production , impair clearance of apoptotic cells and confer downstream effects on activation of other proteases such as MMPs.[38-40] Elastase is critical to initiating the process of neutrophil extracellular trap formation- a form of cell death enhanced in chronic lung disease resulting in the active extrusion of DNA and toxic neutrophil granule products.[41]

NE inhibition is therefore a potentially logical approach in bronchiectasis. Oral and inhaled preparations of NE inhibitor compounds are in clinical development while two oral NE inhibitors have been already trialled in bronchiectasis patients.[42-44] AZD9668 was tested in 38 patients over 28 days. The primary outcome of reducing sputum neutrophil counts was not achieved, but there was a statistically significant 100ml increase in FEV1 and promising trends in quality of life using the SGRQ.[43] A study of 94 patients with the NE inhibitor BAY85-8501 showed no evidence of efficacy in bronchiectasis and has only been reported in abstract form.[44] This is not a promising background against which to develop new drugs, but these studies do not necessarily invalidate the approach of inhibiting NE. For instance, 28-days may be too short a duration to demonstrate effectiveness for an anti-inflammatory treatment; macrolides reduced exacerbations and improved quality of life over 6-12 months in bronchiectasis, but these trials would have been negative if stopped at day 28.[22-25] Further, no evidence has been shown to indicate that the administered doses of AZD9668 or BAY85-8501 were sufficient to inhibit sputum NE activity in bronchiectasis patients.

Support for the concept that NE may be important in bronchiectasis disease progression has recently been provided by a UK study of 433 patients.[30] In this cohort elevated sputum NE activity was associated with a higher exacerbation frequency and a more rapid decline in FEV1. [30] An important finding of this study, however, was that 1/3 of patients with bronchiectasis did not have active sputum NE at baseline.[30] If this were replicated in the above clinical trials, they may be grossly underpowered to illustrate any clinical benefits on the assumption that patients without active NE could not be expected to respond to inhibitor therapy. This argues for a "personalized medicine" approach to future trials of anti-neutrophil therapy.

***Cathepsin C/* dipeptidyl-peptidase I inhibition (DPP1)**

An alternative approach to traditional NE inhibition is the use of inhibitors that target the activation of serine proteases in the bone marrow.[45] DPP1 is a lysosomal cysteine protease that cleaves NE, cathepsin G and proteinase-3, activating them during neutrophil maturation.[45] Activated neutrophil serine proteases are then packaged into granules before the mature neutrophils are released into the systemic circulation. DPP1 inhibitors therefore could theoretically abolish neutrophil serine protease activity in the airway at source.

Two DPP1 inhibitors are currently identified in the clinicaltrials.gov database as being in development for bronchiectasis.[46]

Challenges in the development of DPP1 inhibitors reflect the difficult balance that must be achieved in inhibiting neutrophil functions. Neutrophils are unquestionably damaging in the context of chronic inflammation but are also required for host defence in multiple tissues. Mutations that inactivate the DPP1 gene in humans result in an immunodeficiency called Papillon-Lefevre syndrome (PLS).[47] PLS is characterised by palmoplantar keratoderma and periodontitis. The latter results in the loss of all teeth during childhood.[47]

Initial human trials have now been conducted with DDP1 inhibitors. GSK2793660 was administered to healthy male subjects in a phase 1 trial with escalating doses.[48] While only modest reductions in neutrophil protease activity in blood were observed (approximately 20%) 7 out of 10 subjects in the trial manifested palmar/plantar epidermal desquamation.[48] A single, followed by multiple ascending dose study of the reversible DPP1 inhibitor AZD7986 achieved reductions in plasma NE activity of up to 50% at the highest tested doses. 5 patients in the cohort manifested mild exfoliation of the palms and soles which reversed after treatment discontinuation.[49] A phase 2 trial in patients with bronchiectasis has recently been initiated.[50]

While this mechanism appears promising, the potential adverse effects represent a challenge for large scale testing in RCTs. Patients in longer studies would require careful assessment of dental and skin health. All studies targeting immune responses in bronchiectasis suffer from the challenge of trying to identify "the goldilocks zone" where inflammation is suppressed sufficiently to improve clinical outcomes without overtly suppressing host defence such that infectious complications develop.

CXCR2 antagonism

A further approach to reducing neutrophilic inflammation is to directly reduce the number of neutrophils entering tissues by preventing chemotaxis, or to reduce inflammation by preventing or reducing neutrophil activation. CXCR2 is a chemokine receptor, activated by binding of CXCL1 and CXCL8. Antagonism of CXCR2 has been shown to reduce lung neutrophil recruitment without impairing phagocytosis or oxidative burst, activities partially mediated through CXCR1.[51] A single clinical trial has been completed in bronchiectasis with oral administration of AZD5069 80mg twice daily.[14] In 45 patients completing treatment, this therapy reduced sputum neutrophil numbers by 69% with no difference in the small number of exacerbations over 28 days follow-up.[14] There were 4 infection-related

discontinuations in the AZD5069 group (1 due to pneumonia and 3 exacerbations of bronchiectasis) with none in the placebo group.[14] Studies in humans and non-human primates illustrate an increase in blood cytokines with treatment including the CXCR2 ligands CXCL8 and CXCL1.[14] The clinical significance of this is unknown. Again, 28 days is likely to be too short a period to evaluate clinically relevant effects and larger studies are needed. Additional CXCR2 antagonist compounds are in current clinical development.[52]

Immunomodulatory drugs

Inflammation in bronchiectasis is complex and it is uncertain that targeting neutrophils alone will be sufficient to improve clinical outcomes. A number of additional anti-inflammatory therapies with a wide range of clinical effects are in development or have been tested.

Vitamin D

Vitamin D receptors are found on the majority of inflammatory cells.[32] Vitamin-D has broad-spectrum anti-inflammatory effects, suppressing cytokine production, promoting LL-37 secretion from epithelial cells and enhancing *P. aeruginosa* killing.[53] *In-vitro* observations with vitamin-D have not always translated into clinically meaningful benefits in other diseases.[54] A UK study found that 50% of bronchiectasis patients had vitamin-D deficiency with the most deficient subjects illustrating higher rates of bacterial infection (including *P. aeruginosa*), and a higher rate of exacerbations.[32] Association does not prove causation however, and it is not known if replacement of vitamin-D would improve clinical outcomes in bronchiectasis. Trials of replacement therapy are ongoing and will provide evidence to suggest either a causal association, or whether vitamin D deficiency is a consequence of chronic illness and the accompanying lack of exposure to outdoor sunlight.[55] Trials of vitamin-D replacement are challenging since optimal concentration and replacement dose are unknown.

GM-CSF

Granulocyte-macrophage colony stimulating factor is a glycoprotein secreted by macrophages, T-cells, mast cells, NK cells and epithelial cells and has diverse effects on neutrophils, macrophages and eosinophils.[33] Non-tuberculous Mycobacteria represent a challenging subgroup of bronchiectasis mostly associated with *Mycobacterium avium* and requiring prolonged treatment with antibiotics.[56] Success with >1 year of antibiotic therapy in clearing *M. avium* from sputum varies from 13-86% in reported series. Therefore adjunctive therapy to antibiotics may carry significant benefits. Exogenous GM-CSF *in-vitro* has been shown to enhance intracellular killing of *M. avium*.[57] Onyeji *et al*, demonstrate that GM-CSF treatment augments the antibacterial activity of macrolides in killing *M. avium*.[58] Kim recently demonstrated that patients with NTM pulmonary disease (NTM-PD) had increased levels of anti-GM CSF antibodies versus controls suggestive of a possible mechanism for the requirement of exogenous GM-CSF.[59] Pulmonary alveolar proteinosis is a rare lung disease characterised by the presence of anti-GM CSF antibodies for which replacement treatment is already in clinical use. GM-CSF is therefore one area where rapid trial development is possible.[59]

The role of GM-CSF is not limited to Mycobacteria. GM CSF deficient mice show an increased susceptibility to *P. aeruginosa* infection and defective alveolar macrophage phagocytosis, killing and hydrogen peroxide generation.[60] GM-CSF enhances neutrophil phagocytosis and bacterial killing in critical illness. Ruchaud-Sparagano reported that the addition of GM-CSF to neutrophils from bronchiectasis patients induced increases in superoxide generation and the phagocytosis of zymosan.[33] Whether such addition could reverse abnormalities in diseased airway neutrophils is unknown and requires investigation.

Phosphodiesterase-4 (PDE4) inhibitors/ Roflumilast

There is an important overlap between bronchiectasis and COPD. Up to 50% of bronchiectasis patients meet spirometric criteria for COPD and up to 60% of patients with severe COPD meet radiological criteria for bronchiectasis.[3] The situation is complex as airflow obstruction in bronchiectasis often arises in the absence of cigarette smoking and likely follows a different pathophysiology to that in traditional COPD. Conversely, not all radiological dilatation in COPD is likely to be clinically significant.

Nevertheless, there is interest in whether therapeutic concepts in COPD will be transferable to some patients with bronchiectasis. Roflumilast is a broad-spectrum anti-inflammatory agent that reduces exacerbations in patients with COPD with chronic bronchitis and a high baseline frequency of exacerbations.[61] Since chronic bronchitis is also a characteristic feature of bronchiectasis, there is some logic to considering this for bronchiectasis. There is little other clinical or *in-vitro* data, however, to support the concept directly in bronchiectasis.[62] [59]

Statins

Statins modulate the innate and adaptive immune systems and have powerful anti-inflammatory effects that underlie their benefit in cardiovascular disease.[63] Mouse models show that statin administration protects against multiple bacterial infections.[63] 2 RCTs of statins have been performed in bronchiectasis, both single centre UK studies.[64,65] In the first, atorvastatin 80mg daily was compared to placebo over 6 months in 60 patients. Statin therapy resulted in a 2.2 unit improvement in the Leicester cough questionnaire (LCQ), but was also associated with a significant increase in adverse effects (33% vs 10%).[64] This study enrolled only patients without chronic *P. aeruginosa* infection and so a second study was performed in more severe patients with *P. aeruginosa*. This study was a cross-over trial of 27 patients using the same atorvastatin dose. The primary outcome of improvement in LCQ was not met (mean difference 1.92) but there was a significant improvement in SGRQ.[64] The mechanism of apparent statin benefits is unclear as the first study reported increases in neutrophil apoptosis while the second trial

reported reduced neutrophil activation in statin treated patients.[63,64] Whether these observations are clinically relevant remains to be established. The small sample size of these trials, the inconsistent clinical benefit and the increased rate of adverse events has led to a recommendation against their use in the recent ERS guidelines. Further larger and more focused studies are needed.[4]

Targeting mucociliary clearance and cough

Airway clearance exercises are the mainstay of therapy in bronchiectasis because it is believed that natural mucociliary clearance is impaired.[4] Novel therapies enhancing mucociliary function, mucus hydration and reducing symptoms would be of great clinical value. Therapies used in practice such as hypertonic or isotonic saline, or cysteine derivatives, are supported by minimal data.[4] A large UK trial of hypertonic saline and carbocisteine will commence in 2018 and may provide the necessary supporting data.

There is limited data on the extent and mechanisms of epithelial dysfunction in bronchiectasis which limits the development of therapies that target this aspect of disease. This is an area of intense study in CF, where CFTR corrector therapy is now implemented in clinical practice with striking results, and ion channel targeting therapies are in clinical development.[66] The clinical trials registry identifies a single study proposing the use of CFTR correctors or ENAC inhibitors in bronchiectasis, specifically in the context of primary ciliary dyskinesia.[67] Some bronchiectasis patients have impaired cystic fibrosis transmembrane regulator (CFTR) function that does not meet the diagnostic criteria for CF. The importance of CFTR mutations in “non-CF” bronchiectasis is controversial. . A Spanish study found CFTR mutations in 36% of patients.[68] while French work measured nasal potential differences (NPD) in 122 patients with idiopathic bronchiectasis and a normal sweat test. They found that CFTR mutations were common in patients with bronchiectasis and patients with CFTR mutations and abnormal NPDs were more likely to have

Staphylococcus aureus and *P. aeruginosa* infection, organisms classically associated with CF.[69] A key limitation of this study is the lack of generalizability as the average age of the cohort (45 years) is approximately 20 years younger than most European bronchiectasis cohorts. Additionally, the majority of patients developed symptoms in early adulthood suggestive of an enrichment for patients more likely to have a CFTR related disorder. In contrast King *et al* found only 4 CFTR mutations in 100 non-CF bronchiectasis patients, which is precisely the frequency predicted from the Caucasian carrier frequency of 1 in 25.[70] They therefore concluded no role for classical CFTR mutations in idiopathic bronchiectasis.

It is, however, likely that CFTR dysfunction plays some role in a proportion of non-CF bronchiectasis patients and therefore it is of interest to determine if CFTR correction in those carrying pathogenic mutations can be attempted using drugs such as ivacaftor, lumicaftor or the emerging potentiator/correctors. It is also known that acquired CFTR dysfunction may occur in the absence of CFTR mutations in chronic lung disease, a concept best characterised with cigarette smoke exposure.[71] It is not known but is theoretically possible that CFTR correctors would be effective in the absence of genetic mutations if CFTR dysfunction at the epithelial level was demonstrable in bronchiectasis. Of immediate concern for clinical care and clinical trials is to ensure that CF is appropriately excluded in patients with bronchiectasis. Current guidelines recommend two measurements of sweat chloride and CFTR mutation analysis in adults and children under 40 and those over 40 with clinical features of CF.[5]

ENaC inhibitors aim to rehydrate mucus by preventing sodium hyperabsorption via the ENaC channel, implicated in the dehydration of CF airway surface liquid.[72] The extent to which mucus hydration is an issue in “non-CF” bronchiectasis or whether airway hydration can help to overcome the fundamental cilia defects in PCD remain to be fully evaluated before any logical basis for clinical testing can be pursued.

The need for a personalized approach: understanding bronchiectasis and appropriately targeting therapy

Bronchiectasis is an active field for therapeutic development in areas beyond the treatment of chronic airway infection with antibiotics.(figure 1) Nevertheless, it is likely that no single therapeutic approach will be effective in all patient groups, lessons that should be heeded from other chronic inflammatory lung diseases such as severe asthma and pulmonary fibrosis.[73,74] The clinical and molecular heterogeneity of bronchiectasis must be urgently addressed through detailed endophenotyping studies that will likely permit an improved patient stratification and translate to better clinical trial designs and outcomes. Our current approach to understanding patients groups in bronchiectasis is simplistic. Individual parameters are associated with individual outcomes, for example *P. aeruginosa* infection is associated with mortality and hospital admission risk[75], while NTM infection is associated with middle lobe disease.[56] Nevertheless, even within these groups there is marked heterogeneity that is unresolved and therefore this approach, depicted in figure 2, results in large gaps in knowledge and does not directly lead to effective targeting of therapies. None of the links suggested in figure 2 are specific – for example neutrophilic inflammation becomes more common and more intense as disease becomes more severe, but neutrophils are also found in patients with mild disease.[30] We argue that this current approach is unlikely to lead to effective targeted therapy.

Endophenotyping in bronchiectasis using systems biology, multiomics and the microbiome as a gateway to precision medicine

Patient stratification and the derivation of endophenotypes of clinical relevance may be based on a variety of different variables. The cell-based origin of airway inflammation is a logical start: the majority of patients with bronchiectasis are dominated by chronic airway neutrophilic infiltration however a minority,

up to 1 in 5 illustrate eosinophilic predominance.[76], Larger studies of this latter group are required particularly with the increasing availability of drugs targeting eosinophil recruitment and function including anti-IL5 and anti-IL13 agents in addition to more traditional inhaled corticosteroids.[77]

Our microbiota are in a constant state of fluidity; changing daily through the foods we eat, the environments we live and even people we live and work with.[1] The implications of such change is poorly understood even in the healthy lung and yet to be studied in bronchiectasis. Despite this, there is already a great deal of information available regarding the microbiome in bronchiectasis. Relative abundance and load of pathogens like *Haemophilus* and *Pseudomonas spp.* are linked to neutrophilic inflammation.[31] Rogers, however, showed that patients with *Veillonella* predominance had frequent exacerbations despite lower levels of neutrophilic inflammation.[78] This data clearly hints at a "non-infected" frequent exacerbating population that is unlikely to respond to antibiotic therapy but may respond to alternate forms of immunomodulatory or mucoactive approaches. A limitation of existing microbiota studies is that they predominantly study microbes in isolation, whereas studies that link the microbiota to patient's immunology or other clinical characteristics are more informative[31] We therefore advocate a systems biology and multi-omics approach to attempt to integrate microbiological, inflammatory and phenotypic information in unique way that will allow true patient endotypes to emerge in an unbiased way; endotypes with amenability to targeted therapeutic intervention.[41] Of all the clinical phenotyping studies performed in bronchiectasis to date, the only commonality between them was the emergence of a group dominated by the presence of *P. aeruginosa* which confers poorer prognosis.[75.78] Superimposing immunological, inflammatory and other patterns derived by multiomic approaches including proteomics, transcriptomics and metabolomics will provide even greater clarity and more precision to identifying subgroups of patients with bronchiectasis that appear similar clinically but are fundamentally different. This will influence individual disease trajectory and potentially response to tested therapies. Several

important areas remain largely unexplored in bronchiectasis, there are few large genetic studies outside of CF and PCD, and no studies exploring epigenetics.[80,81]

Precision medicine holds great promise for bronchiectasis: an approach aiming to individualise therapeutic intervention based on multiomic datasets and, integrating this with type and severity of the disease, together with the potential response of an individual patient to a particular treatment regimen. Despite its potential, many challenges exist to ensure it fulfils its promise. With the wide availability of molecular and sequencing technologies that can be applied to the airway we must remain cognisant of the risk of 'getting lost in big data'. To ensure successful translatability of the promise of precision medicine, we must understand its greatest challenges for bronchiectasis. These include clinical challenges such as the current lack of disease signatures and uncertain numbers of patients and samples required for robust analyses. Methodological challenges include a lack of appropriate analytical tools providing the reproducibility and replicability required; this includes difficulties integrating multiomic datasets through existing and rather restrictive bioinformatic platforms. To date there are few studies utilising statistical clustering or data reduction methods to provide comprehensive endotypes. Widely used examples include K-means clustering, latent class analysis and principle component analysis.[79,82,83]

At the patient level, wide geographical and ethnic variation in bronchiectasis exists and may be one of the key challenges. High rates of post-infectious related disease in Asia, the enrichment for bronchiectasis in indigenous populations in the Pacific, a great NTM burden in the Americas and idiopathic disease predominating across Europe are a few examples.[84] These have been comprehensively reviewed elsewhere however such aetiological, microbiological and ethic variation brings about questions related to disease phenotyping and potential endotyping studies that must be considered. Why is disease more severe at a younger age in Asia? What are the environmental and climatic effects on disease, the airway

microbes, infection and the microbiome across regions? What is the impact of innate immune variation on disease? The experience of the RESPIRE 1 and 2 trials, where a study performed predominantly in Asia and Eastern Europe encountered patients with apparently more severe disease but a lower frequency of exacerbations, apparently resulting in discordant trial results, emphasises how important it is to now understand these variations on patient's characteristics.[21]

International disease registries such as the European Multicentre Audit and Research Collaboration (EMBARC) which has enrolled >11000 patients worldwide since 2015, the United States Bronchiectasis Research Registry, and similar initiatives in Australia and India are likely in the next 2-3 years to resolve much of the clinical heterogeneity and allow a great understanding of patient subtypes as well as facilitating recruitment to randomized trials.[7,8,85] Linking these initiatives with translational research should now be a priority.

Treatable traits

Experts in COPD and asthma recently advocated the use of the term "Treatable traits" to describe the spectrum of manifestations of airway disease.[71] Within this definition, the authors included bronchiectasis as a potential "treatable trait". Here we expand this concept to suggest that within bronchiectasis there are also multiple potentially "treatable traits" in individuals with the disease, many of which remain unexplored and untested and, represent a rich source for future work in the field (figure 3). This concept embraces the idea that patients can have multiple treatable traits, and may therefore require complex multicomponent interventions. In addition, endophenotyping approaches accumulate a list of potential "targetable traits" aspects of the biology of bronchiectasis amenable to therapeutic intervention using existing or repurposed drugs which have been discussed in this review. (figure 3)

Conclusions

If this is to be truly "the age of bronchiectasis" therapeutic development must move beyond antibiotics and towards an endophenotyping guided precision medicine approach incorporating immunomodulatory, antimicrobial, mucoactive and disease modifying drugs that target carefully defined patients groups and potentially better clinical trial outcomes.

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Summarized recommendation	Strength of recommendation	Quality of evidence
Perform a minimum bundle of tests including differential blood count, serum immunoglobulins, and testing for ABPA in newly diagnosed patients	Conditional	Very low
Treat acute exacerbations of bronchiectasis with 14 days of antibiotics	Conditional	Very low
Patients with a new isolation of *Pseudomonas aeruginosa* should be offered eradication antibiotic treatment	Conditional	Very low
Do not offer eradication antibiotic treatment to patients following new isolation of pathogens other than P. aeruginosa.	Conditional	Very low
Do not offer inhaled corticosteroids for the treatment of bronchiectasis	Conditional	Low
Do not offer statins for the treatment of bronchiectasis	Strong	Low
Offer long term antibiotic treatment for patients with three or more exacerbations per year*	Conditional	Moderate
Offer mucoactive treatment for patients with difficulty expectorating sputum and poor quality of life where standard airway clearance techniques have failed to control symptoms	Conditional	Low
Do not offer recombinant DNase for the treatment of bronchiectasis	Strong	Moderate
Do not routinely offer long acting bronchodilators for patients with bronchiectasis	Conditional	Very low
Offer long acting bronchodilators for patients with significant breathlessness on an individual basis	Conditional	Very low
Do not offer surgical treatments with the exception of patients with localised disease and high exacerbation frequency despite optimal medical care	Conditional	Very low
Patients with chronic productive cough or difficulty expectorating should be taught airway clearance techniques	Conditional	Low
Patients with impaired exercise capacity should participate in pulmonary rehabilitation and take regular exercise	Strong	High

Table 1. Summary of recommendations from the recent European Respiratory Society guidelines for the management of adult bronchiectasis.[4] Guideline recommendations have been modified from their original wording for brevity and clarity. *additional recommendations are made relating to circumstances where inhaled, oral or macrolide antibiotics may be used. Please refer to the guidelines for full details.[4]

Investigational drug	Phase	Trial design	Primary outcome/objective	Duration	Number of patients	Single or Multicentre	Locatio
Recombinant GM-CSF	I	Single and multiple ascending dose studies in healthy subjects	Safety	28 days	42	Single	, UK
Human Mesenchymal Stem cells	I	Non-randomized safety evaluation	Safety	Single infusion with up to 48 week follow-up	6	Single	Miami,
Neutrophil elastase inhibitor: CHF6333	I	Single and multiple ascending dose studies in healthy subjects	Safety	15 days	72	Single	Belgiu
Cathepsin-C inihibitor GSK2793660	I	Single and multiple ascending dose studies in healthy subjects	Safety	18 days	33	Single	UK
Cathepsin-C inihibitor INS1007	II	Double blind randomized placebo controlled trial	Time to the first exacerbation	24 weeks	240	Multi-centre	World
Roflumilast	II	Open label trial	Change in CASA-Q	16 weeks	25	Single	South Korea
N-aceylcysteine	III	Randomized, open label	Frequency of acute exacerbations	12 months	150	Single	China
ENaC inhibitor*	III	Randomized crossover study	Change in FEV1 and safety	28 days	150	Multi-centre	Worldw

Theophylline	III	Randomized blinded placebo controlled trial	St Georges Respiratory Questionnaire	24 weeks	100	Single	China
Vitamin-D	III	Randomized blinded placebo controlled trial	Time to first exacerbation	1 year	200	Single	China
Neutrophil elastase inhibitor: BAY85-8501	III	Randomized double blind placebo controlled trial	Safety	56 days	94	Multi-centre	Worldv
OM-85 (extracted of multiple bacteria)	III	Randomized placebo controlled trial	Percentage of patients free from exacerbations	1 year	244	Multi-centre	China

Table 2. Summary of selected randomized controlled trials registered in public databases which are active, recruiting or completed but not yet published. We have only included studies not evaluating antibiotics and studying stable patients with bronchiectasis or studies of novel drugs in healthy subjects where the term bronchiectasis was included in the registration indicating these patients as the target population. *specific for patients with bronchiectasis due to primary ciliary dyskinesia.

Figure Legends

Figure 1: A summary of emerging therapies for bronchiectasis in active clinical development.

Figure 2: Current classification of bronchiectasis. The figure demonstrates that patients can be classified into multiple different subcategories based on multiple characteristics. Characteristics that have been well studied and linked to clinical outcomes (boxed pink) and those that have been studied but have not been linked with a specific outcome or clinical phenotype (boxed grey) are illustrated.

Figure 3: Bronchiectasis 'traits' divided into those 'treatable' with current therapies (left hand panel), 'targetable' through future endo-phenotyping approaches (right hand panel) and 'other factors' recognized to have potential effects on bronchiectasis (bottom panel).