



Bronchiectasis 2

Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity

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This is the second in a Series of two papers about bronchiectasis

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Bronchiectasis is characterised by pathological dilation of the airways. More specifically, the radiographic demonstration of airway enlargement is the common feature of a heterogeneous set of conditions and clinical presentations. No approved therapies exist for the condition other than for bronchiectasis caused by cystic fibrosis. The heterogeneity of bronchiectasis is a major challenge in clinical practice and the main reason for difficulty in achieving endpoints in clinical trials. Recent observations of the past 2 years have improved the understanding of physicians regarding bronchiectasis, and have indicated that it might be more effective to classify patients in a different way. Patients could be categorised according to a heterogeneous group of endotypes (defined by a distinct functional or pathobiological mechanism) or by clinical phenotypes (defined by relevant and common features of the disease). In doing so, more specific therapies needed to effectively treat patients might finally be developed. Here, we describe some of the recent advances in endotyping, genetics, and disease heterogeneity of bronchiectasis including observations related to the microbiome.

Introduction

Bronchiectasis is defined as permanent enlargement of the airways,¹ and is mostly the result of an intrinsic airway pathology resulting in dilation. Multiple causes of bronchiectasis and a broad array of clinical presentations exist.² The extent of bronchiectasis can range from focal disease (limited to one segment or lobe) to diffuse disease (involving both lungs and all lobes). Bronchiectatic findings range from subtle dilation to cystic changes in the airways. Some patients will be asymptomatic and the bronchiectasis is discovered unexpectedly, whereas others will have daily symptoms of cough and sputum production with periodic exacerbations.³ The diagnosis of bronchiectasis is increasing worldwide. Previously classified as a rare or orphan disease, bronchiectasis has now been reported at rates of up to 566 per 100 000 population with an incidence that has increased by 40% in the past 10 years.⁴

Despite having its own diagnostic code, there are no medications or therapies approved by regulatory authorities in the USA or Europe for most cases of

bronchiectasis. The exception is bronchiectasis due to cystic fibrosis, for which several approved medications exist, but none are approved as treatments for bronchiectasis of other causes.⁵ However, guidelines that recommend treatments for bronchiectasis are available,⁵ and reports have shown that some therapies are associated with clinical benefit,^{6,7} suggesting that we need to improve our ability to identify those patients with bronchiectasis.^{8,9} The pathway to more precise treatment will require a better understanding of patients beyond imaging studies. Here, we review recent studies, particularly focusing on the past 2 years, that have attempted to better describe patients according to a heterogeneous group of endotypes (defined by a distinct functional or pathobiological mechanism¹⁰) or clinical phenotypes (defined by relevant and common features of the disease¹¹).

Pathophysiology of disease

The list of conditions known to cause or be associated with bronchiectasis is long, but most have common features that lead to the remodelling and dilation of the airways. A useful pathophysiological pathway has described the process as a cycle of events promoting impaired mucociliary clearance and retention of airway secretions. These events disrupt the host's defences and render the airways more susceptible to establishment of chronic infection. The persistence of bacterial pathogens incites an inflammatory response that results in injury and pathological remodelling of the airways leading to bronchiectasis. Each step begets the next, resulting in a persistent and progressive process over time. This model has worked well to describe how numerous conditions enter into the cycle: patients with cystic fibrosis and primary ciliary dyskinesia have impaired mucociliary clearance; immune deficiency can result in

Search strategy and selection criteria

We searched PubMed using the search terms "bronchiectasis", "endotype", "genotype", "microbiome", and "heterogeneity". We focused on papers and reviews published from Jan 1, 2010 to March 1, 2018 in English. We also searched author names of key people in the bronchiectasis field. From key papers, we reviewed reference lists to find additional pertinent papers and to redefine search terms. For the concept of endotyping, we searched this term in combination with other major pulmonary diseases (eg, asthma, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis) to look for similar categorisations.

recurrent and persistent infection; injury to the airways, either because of severe infection or mechanical injury (eg, toxic inhalation or chronic aspiration) can result in an impaired healing of the airways, and so on. However, interactions are far more complex with each pathophysiological step contributing to all others. This process can be better described as a vortex (figure 1). The vortex concept might better explain why individual treatments (eg, antibiotics or anti-inflammatories) in isolation have only modest effects on clinical outcomes in bronchiectasis. Rather than breaking a vicious cycle, which would be expected to halt disease, antibiotics, for example, only affect one component of the vortex suggesting that inflammation and lung damage can be sustained by other stimuli. This model argues for multimodal treatment that addresses all aspects of the disease.

How this pathophysiological model results in dilation of the airways and why such heterogeneity in the extent of the disease exists are less well understood. A simple explanation is that impaired mucociliary function results in an accumulation of material that obstructs and stents the airway (material collects in the airways and exerts an outward pressure on the wall) while remodelling occurs. Another hypothesis can be found in the study of polycystic kidney disease in which a non-motile ciliary abnormality in renal epithelial cells results in cellular hypertrophy and hyperplasia, and cyst formation.¹² Because some patients with polycystic kidney disease also have bronchiectasis,¹³ this co-occurrence suggests there could be a link between cilia, cellular signalling processes, and bronchiectasis. An animal ciliary knockout model of polycystic kidney disease showed loss of airway motile cilia and bronchial remodelling in the absence of inflammation, but with proliferation of facultative progenitor cells.¹⁴ Such a role for ciliary function might offer a commonality among the varied causes of bronchiectasis.

The radiographic features help to explain why some patients will have focal disease (eg, because of severe injury) rather than diffuse (eg, primary ciliary dyskinesia), or why some have disease in the lower lobes (eg, recurrent aspiration). Although some diagnoses have easily available and interpretable diagnostic testing (such as cystic fibrosis), others are less easily established. This diagnosis still might not be sufficient in defining which patients are likely to respond to specific therapies. Alternative characteristics (eg, genotyping or biomarkers) might better characterise patients to understand how best to develop and use therapies.

Endotypes and genotypes

Although most patients will be diagnosed with idiopathic bronchiectasis, indicating that the cause could not be found following testing, reviewing conditions with well known, genetics-based pathways offers

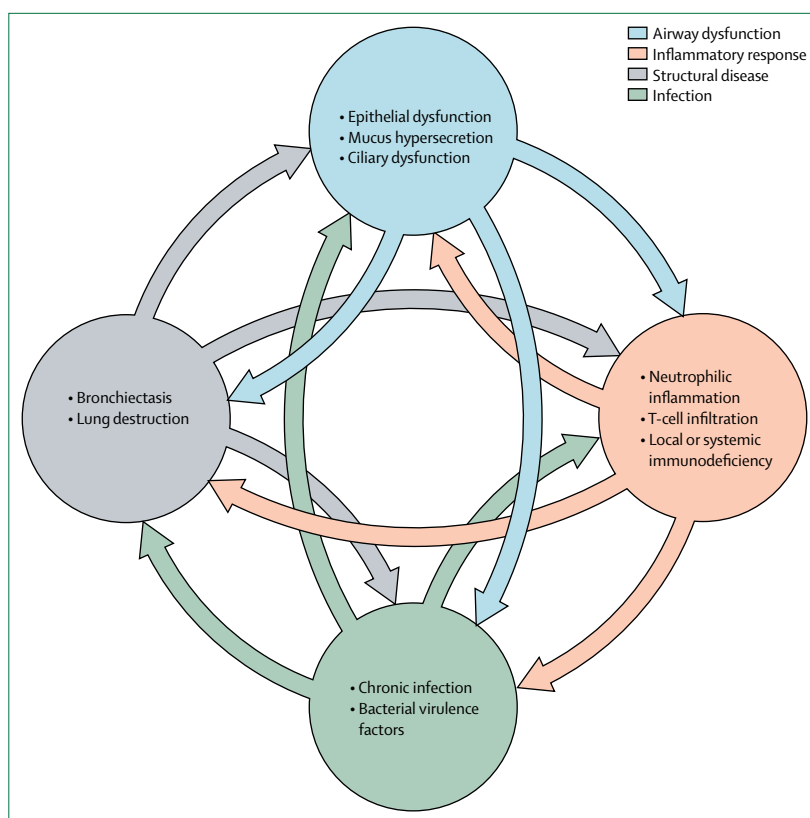


Figure 1: Model describing the pathogenesis of bronchiectasis

A cycle of events that promote a persistent and progressive process over time. Impaired mucociliary clearance and retention of airway phlegm disrupts normal host defences, rendering the airways susceptible to infection, which can become persistent. This process, in turn, incites an inflammatory response causing injury and abnormal remodelling of the airways, leading to bronchiectasis.

insights into understanding the underlying mechanisms of bronchiectasis pathogenesis. These insights can aid in the development of specific treatment regimens. However, the interactions between genetics, endotypes, environment, and therapeutic interventions can vary. In asthma, for example, studies focused on genetic risk loci have not yielded a clear pathway to therapeutic intervention, whereas classification based on inflammatory endotypes can correlate with effective, specific anti-inflammatory therapies.¹⁵

Cystic fibrosis

Cystic fibrosis serves as the prime example of how disease categorisation based on genotype can drive effective therapeutic intervention. Cystic fibrosis is primarily a disorder of mucociliary clearance caused by altered epithelial ion transport. Well characterised biomarkers exist, such as sweat chloride and trans-epithelial potential difference assays, which have been useful in the diagnosis and research assessment of therapeutic response.¹⁶ Discovery of the causative gene for cystic fibrosis in 1989 led to increasing knowledge of the protein product, cystic fibrosis transmembrane conductance regulator (CFTR). This included its

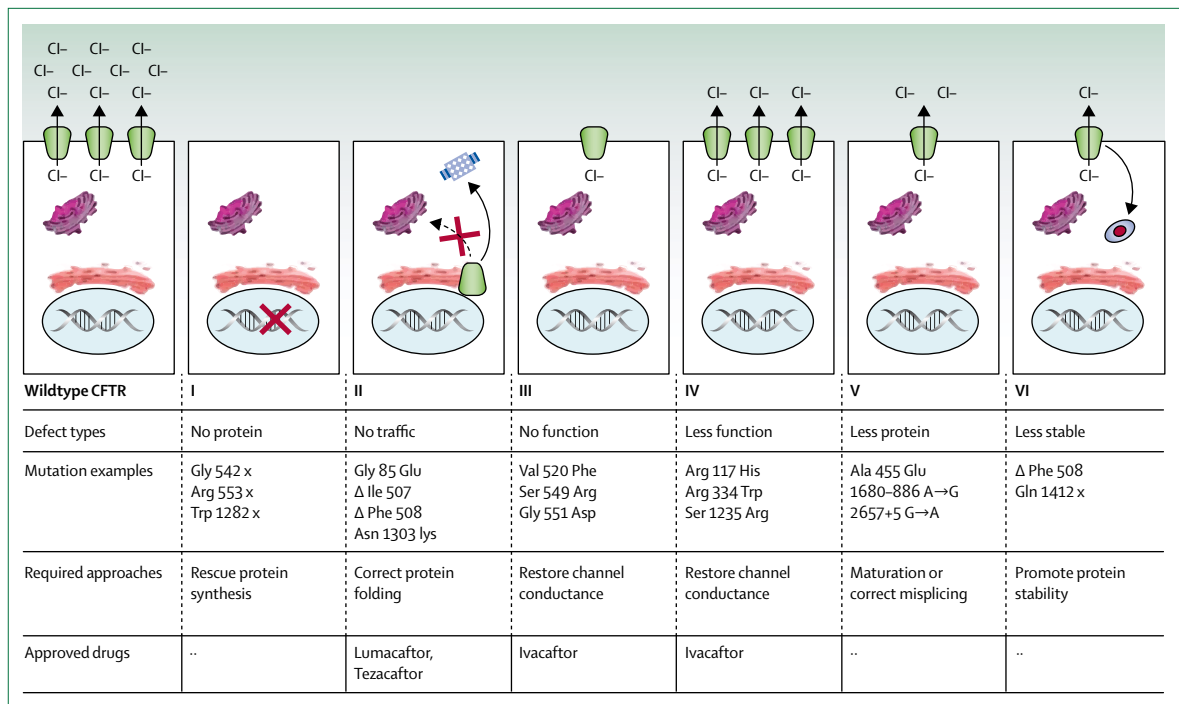


Figure 2: CFTR mutation classification

CFTR mutation classification based on molecular defect. These molecular defects correspond to therapeutic approaches to restore the quantity of protein or its function, or both resulting in genotype specific CFTR modulator drugs used alone (ivacaftor) or in combination (lumacaftor–ivacaftor, tezacaftor–ivacaftor). Reproduced from Lopes-Pacheco.¹⁹ CFTR=cystic fibrosis transmembrane conductance regulators. Cl=chloride ion.

structure, function, and the protein synthesis pathway from nucleus to insertion, and proper functioning in the epithelial apical membrane.^{17,18} The correlation between specific genetic mutations and their effect on CFTR quantity and function has led to remarkable genotype-specific treatment that can substantially improve the clinical course of bronchiectasis and other manifestations of disease (figure 2). Although airway dilation can remain, airway inflammation, secretion clearance, and control of infection can all improve with CFTR modulator therapy.^{20,21}

Primary ciliary dyskinesia

Primary ciliary dyskinesia is another genetic disorder of mucociliary clearance characterised by disordered function of motile cilia. Bedside measurement of nitric oxide production is a useful biomarker of ciliary motility,²² but it must be emphasised that primary ciliary dyskinesia genotypes associated with normal concentrations of nasal nitric oxide have been described.²³ Measurement of nasal nitric oxide production and high-speed video assessment of ciliary beat characteristics might be useful markers of drug efficacy in future clinical trials.²⁴ In contrast to the monogenic cause of cystic fibrosis, the assembly and regulation of ciliary proteins is under the control of multiple genes.²⁵ Although electron microscopic examination of cross-sectional cilia anatomy lacks sufficient sensitivity and specificity to be a useful diagnostic test,

correlation has been noted in research settings between mutated genes and structural abnormalities (figure 3). As drug development for primary ciliary dyskinesia advances, this relationship of genotype-function or structure-function might prove useful for drug targeting similar to the path that CFTR modulator therapeutics development has taken in cystic fibrosis.

Immune deficiencies

Bronchiectasis is a common manifestation of many primary immune deficiencies and disorders of immune regulation. These conditions can be subdivided roughly on the basis of the primary immune cells of origin. Biomarkers that can be useful in diagnosis and assessment of treatment include lymphocyte phenotyping with delineation of T cell, B cell, and natural killer cell numbers, quantitative immunoglobulin concentrations, and specific antibody responses to protein and polysaccharide antigens. Humoral immune deficiencies account for approximately 70% of all primary immune deficiencies and the majority of primary immune deficiency-associated causes of bronchiectasis.²⁷ Although abnormally low immunoglobulin concentrations could point toward this subgroup, knowledge of the underlying genetic causes are of increasing importance for directing specific therapies or for early identification of patients who would benefit from bone marrow transplantation. Common variable immune deficiency, the most

commonly diagnosed immune deficiency characterised by substantial reductions in IgG and sometimes reductions in IgA or IgM, or both, and presentation later in life with recurrent pyogenic sinopulmonary infections, is clinically and genetically a heterogeneous disorder.²⁸ X-linked agammaglobulinaemia is caused by mutations in the Bruton's tyrosine kinase gene and can result in a profound humoral immune deficiency.²⁹ However, even X-linked agammaglobulinaemia can have a variable clinical phenotype on the basis of genotype, with adults having a higher proportion of splice-site mutations and lower proportion of frameshift mutations than children.³⁰ The autosomal dominant hyperimmunoglobulin E syndrome (Job's syndrome) is another example of a rare primary immune deficiency that can be identified by its characteristic of markedly elevated IgE concentrations and clinical findings of eczema, recurrent skin and pulmonary infections, skeletal abnormalities, and coarse facial features. However, with this disease, the high IgE concentration is more of a disease marker than a pathway indicator. This disease has been better defined by identification of mutations in the signal transduction and activator of transcription 3 (*STAT3*) gene.³¹ *STAT3* is important for several key airway defence mechanisms including T helper 17-based cytokine signalling leading to up-regulation of antimicrobial peptides. It is also considered to have a role in proper remodelling after epithelial injury by directing differentiation of airway basal cells into ciliated cells and away from mucus secreting epithelial cells.³² Mutations in *STAT3* affecting these pathways are likely to account for the high prevalence of bronchiectasis and cystic changes (pneumatoceles) seen in this disease. With the availability of whole exome sequencing, it is probable that mutations in genes affecting immune function and regulation will be identified. These mutations could account for unsuspected underlying systemic immune causes for patients with recurring respiratory tract infections leading to bronchiectasis with atypical late presentations diagnosed in adulthood.^{33,34}

Autoimmune diseases

Several autoimmune diseases, most notably rheumatoid arthritis and inflammatory bowel disease, are associated with bronchiectasis. These conditions typically have predominant manifestations outside of the respiratory tract. Biomarkers such as rheumatoid factor, C-reactive protein, anti-nuclear cytoplasmic antibodies, and anti-*Saccharomyces cerevisiae* antibodies might be helpful in identifying these diseases in patients presenting with joint or bowel symptoms; however, they are not so helpful in characterising the associated airway disease. Although infections might be common in bronchiectasis associated with these disorders, the inflammatory component frequently predominates. In the case of ulcerative colitis-associated bronchiectasis, the airway

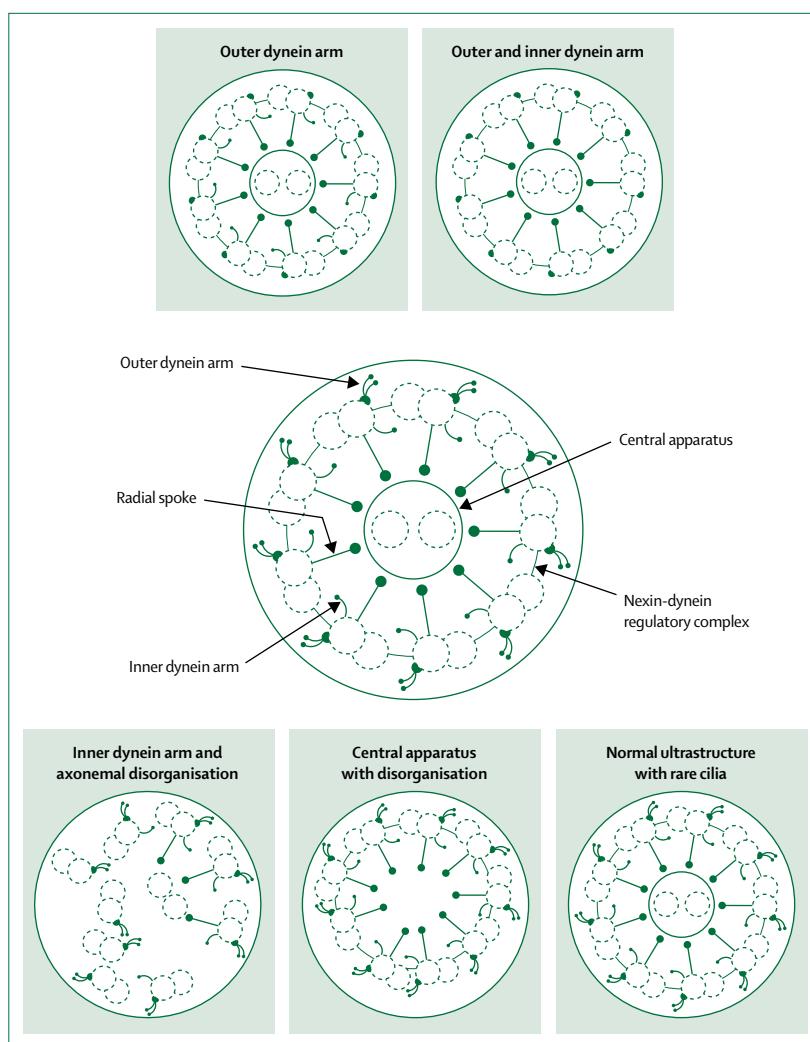


Figure 3: Ciliary dyskinesia gene classifications

Defects in cilia genes can be classified on the basis of ultrastructural effects seen on cross-sectional examination of cilia with electron microscopy. Note that some genes can be mutated without obvious structural abnormalities. Genes associated with the outer dynein arm include *DNAH5*, *DNAI1*, *DNAI2*, *TXNDC3*, *DNAL1*, *ARMC4*, *CCDC114*, and *CCDC151*. Genes associated with the inner and outer dynein arm include *LLRC6*, *DNAAF1*, *DNAAF2*, *DNAAF3*, *CCDC103*, *ZMYND10*, *HEATR2*, *DYX1C1*, *SPAG1*, and *C21orf59*. Genes associated with the inner dynein arm and axonemal disorganisation include *CCDC39* and *CCDC40*. Genes associated with the central apparatus are *HYDIN* (*RSPH4A* and *RSPH* with disorganisation). Genes associated with normal ultrastructure are *DNAH11*, *CCDC164*, *CCDC65*, and *RSPH1* (*CCNO* and *MCIDAS* with rare cilia). Modified from Horani and Ferkol.²⁶

findings of cobblestoning, ulcerations, and mucosal lymphoplasmocytic infiltration can mimic bowel findings. These pulmonary manifestations can respond to anti-inflammatory agents such as inhaled or systemic steroids; however, some cases might require tumour necrosis factor α blockade (once infection is identified and controlled with antibiotics) or other immunomodulatory drugs commonly used to treat bowel inflammation to control the progression of bronchiectasis.³⁵ Causative genes have not been identified for rheumatoid arthritis and inflammatory bowel disease (ulcerative colitis). However, for inflammatory bowel disease,

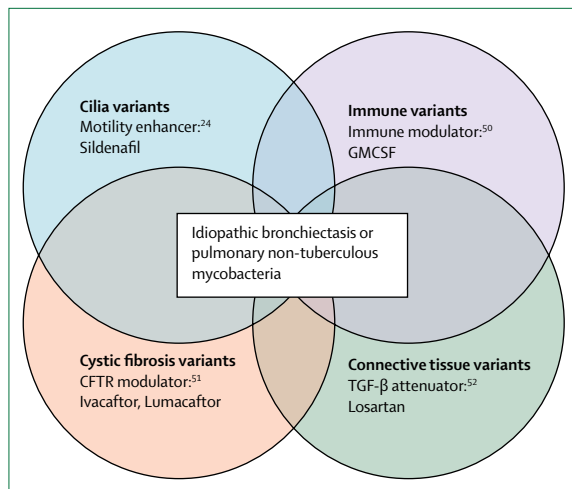


Figure 4: Potential endotypes for patients with idiopathic bronchiectasis with pulmonary non-tuberculous mycobacteria infections

Characterisation with biomarker measurements of sweat chloride, nasal nitric oxide, ciliary beat frequency, and body morphometrics coupled with the presence of relevant genetic variants could allow therapeutic targeting on the basis of the predominant endotype. CFTR=cystic fibrosis transmembrane conductance regulators. GMCSF=granulocyte-macrophage colony-stimulating factor. TGF- β =transforming growth factor- β .

associated genetic risk loci have been reported including *NOD2*, *ATG16L1*, *IRGM*, *IL23R*, *TNFSF15*, and *HLAD-QA1*. Further investigation is needed to establish whether these loci correlate with airway manifestations and can lead to more specific therapeutic interventions.³⁶

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis represents a unique overlap between immune dysregulation and obstructive airway diseases such as asthma and cystic fibrosis. Although allergic bronchopulmonary aspergillosis is associated with filamentous fungi in the airway, biomarkers of the allergic inflammatory response (eg, eosinophilia, total IgE, serum precipitins, and *Aspergillus*-specific IgE with IgG as a marker of *Aspergillus fumigatus* exposure) are prominent in the diagnostic criteria.^{37,38} The bronchiectasis is frequently proximal and might have an exaggerated saccular, plugged appearance. A 2016 study, comparing patients with allergic bronchopulmonary aspergillosis with those who have atopic asthma and healthy participants, identified allergic bronchopulmonary aspergillosis-associated single nucleotide polymorphisms in *TLR3*, *IL4R*, and *IL13*.³⁹ These polymorphisms and other reported potential genetic susceptibility loci could be helpful in elucidating pathways and pointing to more specific therapies.

Chronic obstructive pulmonary disease (COPD) and asthma

The general relationship between asthma, COPD, and bronchiectasis remains unclear as to directionality of development.⁴⁰ Bronchiectasis can be present in both

asthma and COPD and has been associated with more advanced stages of these diseases.^{41,42} Conversely as bronchiectasis progresses, increasing degrees of chronic airway obstruction can be seen and labelled as COPD and some patients with bronchiectasis could have eosinophilia, elevated IgE, and at least partly reversible airway obstruction suggesting an asthmatic component to their disease. Bronchiectasis has been historically under-recognised; therefore, some of the overlap represents historical misdiagnosis. Endotyping to guide therapy has garnered much attention in asthma management and biomarkers (eg, eosinophilia or increased IgE) could be useful in identifying patients with bronchiectasis who might benefit from directed anti-inflammatory treatment. The prime example of genetic overlap between COPD and bronchiectasis is α 1-antitrypsin deficiency in which a correlation exists between the amount of the biomarker, the genotype, and disease severity.

Idiopathic bronchiectasis associated with non-tuberculous mycobacteria (NTM)

Since the late 1980s, there has been increasing recognition of a population of patients with idiopathic bronchiectasis, many of whom are chronically infected with NTM.⁴³ This group of patients are reported predominantly as women who are post-menopausal and non-smokers with no known predisposing factors who present with chronic cough.⁴⁴ They share characteristics with other endotypes, notably a high prevalence of CFTR mutations and evidence of ciliary dysfunction,^{24,45,46} but they do not meet diagnostic criteria for cystic fibrosis or primary ciliary dyskinesia. Such observations suggest the cause of the condition is likely to be multifactorial in which mucociliary clearance defects could play a key role.

These patients have physical characteristics such as a tall, asthenic morphotype, scoliosis, pectus excavatum, mitral valve prolapse, and dural ectasia, which overlap with heritable connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome.^{46,47} Both bronchiectasis and pulmonary NTM infections have been noted in a well characterised population with these heritable connective tissue disorders.⁴⁸ Conversely, key characteristics such as bronchiectasis, NTM infection, and connective tissue disease features have been reported in a high proportion of first and second degree relatives of carefully phenotyped patients with idiopathic bronchiectasis and pulmonary NTM infections, strongly suggesting a genetic component to the disease.⁴⁸ Whole exome sequencing, with use of a candidate gene analysis of low frequency, potentially protein-altering variants, identified a statistically significantly higher prevalence of variants in connective tissue disease-associated genes and in mucociliary clearance-associated (CFTR and cilia-related) genes in probands affected by NTM and family members affected and unaffected by NTM

	Age of onset	Radiology	Microbiology	Symptoms or features	Physiology or lung function
Idiopathic	Women who are post-menopausal at any age	Any radiological pattern	<i>Pseudomonas aeruginosa</i> , <i>Haemophilus influenzae</i> , any pathogens or none	Any	Any
Post-infective bronchiectasis	Any	Any pattern, unilobular	Any pathogens or none	Should typically have onset of symptoms soon after a severe infection	Any
Connective tissue disease	Any	Any	Any	Poor prognosis or rapidly progressive, features of systematic disease ⁵⁴	Airflow obstruction (but other patterns seen)
Immune deficiency	Primary immune deficiency often at young age, secondary immune deficiency at any age	Lower lobe	Any	Frequent exacerbations, pneumonia, non-respiratory infections	Airflow obstruction
Allergic bronchopulmonary aspergillosis	Any	Central bronchiectasis, infiltrates	Typically <i>Staphylococcus aureus</i> ⁵⁵	Thick sputum, wheeze, recurrent exacerbations, background of asthma	Airflow obstruction
Non-tuberculous mycobacteria	Women who are post-menopausal at any age	Middle lobe and lingula bronchiectasis, tree in bud, nodular changes	In addition to non-tuberculous mycobacteria, can have typical bacteria such as <i>P aeruginosa</i>	Dry bronchiectasis, chronic cough, malaise, weight loss, systemic features, low body-mass index, scoliosis, pectus excavatum	Any
Primary ciliary dyskinesia	Usually presents in childhood	Middle or lower lobes	<i>H influenzae</i> , any	Chronic rhinosinusitis, recurrent otitis media	Any
Chronic obstructive pulmonary disease	Smokers or ex-smokers older than 40 years	Lower lobe cylindrical bronchiectasis	Any or no bacterial infection	Recurrent exacerbations, sputum production	Airflow obstruction (bronchiectasis more common with more severe airflow obstruction) ⁵⁶
Inflammatory bowel disease	Any	Any lobes affected, bronchiolitis, could include other features of inflammatory bowel disease-associated lung disease	Often no pathogens isolated	Gross bronchorrhea, which is often responsive to corticosteroids	Airflow obstruction
Cystic fibrosis	Young age of onset but can present in adulthood	Upper lobes	<i>P aeruginosa</i> , <i>S aureus</i> , others	Rhinosinusitis, infertility, pancreatitis, malabsorption, gastrointestinal symptoms	Airflow obstruction

Note that patients do not always present with classic features and therefore the absence of these signs cannot be used to exclude a specific cause in bronchiectasis. Consensus guidelines recommend standard testing irrespective of clinical phenotype.

Table: Clinical features associated with specific causes in bronchiectasis

compared with a healthy control reference population.⁴⁹ Many of the family members unaffected by NTM had bronchiectasis or connective tissue disease traits, or both. A higher prevalence of variants in genes related to systemic mycobacterial control distinguished family members with pulmonary NTM from those without NTM. Using a combination of phenotypic characteristics (tall, asthenic morphotype, and dural ectasia), biomarkers (sweat chloride, nasal nitric oxide, and ciliary beat frequency), and genetic analysis, it might be possible to place patients with idiopathic bronchiectasis into key endotypes that could eventually point to a role for directed therapeutic interventions to address the underlying predisposing factors for disease development and progression. Theoretically, drugs which modulate CFTR function, modulate ciliary beating characteristics,

mitigate vascular and other sequelae of connective tissue disorders, or enhance relevant systemic immune pathways could alter host susceptibility and improve the disease course in patients with idiopathic bronchiectasis and chronic NTM infections (figure 4).

Disease heterogeneity beyond causes: clinical phenotypes

Assessing patients with bronchiectasis requires knowledge of the heterogeneity of clinical presentation and variable clinical course. Patients with apparently mild symptoms at presentation could still have adverse prognostic factors and have rapid progression of disease, whereas others with seemingly severe symptoms at the outset might be easily managed and have a good prognosis.⁵³ A multidimensional approach to patient

assessment should incorporate clinical history, physical examination, appropriate laboratory testing, microbiology, and functional assessments. Some causes of bronchiectasis have specific clinical presentations or have characteristics that indicate the underlying causal diagnosis (table) and inform use of diagnostic testing.^{57–59} However, many of these features remain non-specific and so efforts have been made to identify clinically recognisable sets of observable characteristics that link to clinical outcomes (ie, clinical phenotypes).⁶⁰

Exacerbations of bronchiectasis, defined clinically as worsening of the usual respiratory symptoms,⁶¹ are important events in the natural history of bronchiectasis. Patients with three or more exacerbations a year had worse health status, were more likely to be hospitalised for treatment, and had increased mortality.⁶² Most importantly, frequent exacerbation was identified as a true phenotypic trait because the majority of patients consistently had these exacerbations over time, whereas patients who did not have a history of exacerbations rarely had events during follow-up. As shown for COPD⁶³ and cystic fibrosis,⁶⁴ a history of exacerbations in patients with bronchiectasis is the strongest predictor of future events, whereas individual comorbidities, bacteriology, severity of disease determined radiographically, and other variables explained only a very small amount of the variance in exacerbation frequency.⁶² This finding suggests that what leads a patient to have frequent exacerbations is not fully understood. Therefore, in clinical practice, a history of exacerbations is the only variable that can be confidently used for prediction of future events.

Various studies have attempted to use statistical clustering techniques to identify subgroups of patients with bronchiectasis with different characteristics.^{65,66} Most identified clusters have been based on current age, age of onset of disease, and disease severity, and none have been replicated in independent cohorts suggesting that they are not true phenotypes. The major phenotype identified in all cohorts of patients with bronchiectasis is chronic infection with *Pseudomonas aeruginosa*. Patients with chronic infection due to *P aeruginosa* have an increased burden of disease including a higher frequency of exacerbations, worse health-related quality of life, increased risk of hospital admissions, and increased mortality.^{67–69} *P aeruginosa* can exhibit adaptive behaviours allowing it to survive in a hostile environment such as the human airways, and the production of biofilms obstructs exposure of the bacteria to antibiotics and phagocytes.^{70,71} *P aeruginosa* also produces virulence factors that allow it to evade phagocyte killing and slow ciliary beat frequency, further allowing it to maintain its presence.⁷² The mere presence of *P aeruginosa* has not been sufficient to define patients who benefit from aerosolised suppressive antibiotic therapy;⁸ however, because there are patients who do benefit from inhaled antibiotics,⁶ this

suggests there could be other factors (eg, bacterial abundance) that are more predictive.

Patients who have so-called dry bronchiectasis do not produce daily sputum, a syndrome that has been long recognised. A case series published in 1933 describes 20 cases arising from infections in childhood in whom bronchiectasis was associated with cough and occasional haemoptysis without prominent sputum production.⁷³ Such patients have lower symptom scores but surprisingly have a higher mortality than patients who have chronic infection or daily sputum.⁶⁵ Dry bronchiectasis has been traditionally associated with NTM infection.

By contrast, a group of patients have been observed who present with excessive sputum production but without the consistent finding of bacteria in sputum cultures. Such patients are described as having sterile bronchorrhea although modern molecular microbiology techniques teach us that sputum samples are never sterile.⁷⁴ This group has been typically associated with inflammatory bowel disease, in whom sputum samples contain neutrophils and necrotic material but do not have detectable pathogens.⁷⁵ Further research is required to identify other meaningful clinical phenotypes that are independent of cause.

Microbiology and the microbiome

Chronic bacterial infection is a characteristic in many patients with bronchiectasis. The term chronic infection is preferred to colonisation because colonisation implies a benign process whereas chronic infection is more reflective of the long-term interaction between microorganisms and the host leading to progressive tissue damage. Sputum culture remains an important part of management because the presence of some organisms has prognostic implications. This information can help guide treatment of exacerbations and could identify patients for whom long-term suppressive antibiotic therapy might be effective.⁷⁶ Traditional culture methods for bacteria show that nearly 80% of patients will regularly grow pathogens in sputum samples, the most frequent being *P aeruginosa* and *Haemophilus influenzae*, but other Gram-negative (eg, *Moraxella catarrhalis*, *Escherichia* species, and *Klebsiella* species) and Gram-positive (eg, *Streptococcus pneumoniae* and *Staphylococcus aureus*) bacteria are isolated frequently.⁷⁷ Although *H influenzae* and *P aeruginosa* are the most common organisms identified in European studies, the US bronchiectasis registry reported high proportions of isolation of NTM (50%) and *P aeruginosa* (33%), whereas *H influenzae* was relatively uncommon (8%).⁷⁸ The reason for the higher frequency of NTM in the USA is not clear, but might reflect some element of selection bias as many US registry sites are also referral centres for NTM lung disease.⁷⁸

The understanding of chronic infection in bronchiectasis is evolving with the advent of sequencing

technologies that allow a more comprehensive profiling of the bacterial communities in the lung, termed the microbiome. A microbiome analysis of healthy airways reveals a rich, diverse community of bacteria that are present in low abundance.⁷⁹ It is premature to define the flora of the airways as healthy, as some, or all, of these microorganisms could represent transient populations introduced through microaspiration. Across many respiratory diseases it has been shown that disease is associated with a loss of bacterial diversity, (ie, through the loss of important bacterial taxa), or by the dominance of a single taxon or small group of taxa.⁸⁰ The dominance of a single taxon or small group of taxa is referred to as a loss of evenness of the microbiota, whereas the loss of diversity is referred to as a loss of richness. Measures of richness and evenness, or composite diversity measures such as the Shannon-Wiener diversity index have a positive linear correlation with lung function in bronchiectasis,⁸¹ although it cannot be stated whether this result is causal or due to frequent antibiotic exposure as studies to date have been mostly cross-sectional. The proteobacteria, which include *Pseudomonas* and *Haemophilus*, come to dominate the diseased dysbiotic airway in bronchiectasis⁸² and have been associated with more neutrophil-mediated inflammation and exacerbations.⁸⁰ However, there is a subgroup of patients with microbiota dominated with firmicutes (eg, the anaerobe *Veillonella*) that have frequent exacerbations despite lower amounts of neutrophilic inflammation.^{83–85}

There is still much to learn about microbiota changes relevant to the development of bronchiectasis and its progression. The importance of early persistent bacterial infection in cystic fibrosis and primary ciliary dyskinesia is well established; interest is growing in persistent bacterial bronchitis in children, which could lead to development of bronchiectasis, suggesting that aggressive treatment with antibiotics could ultimately prevent this development from happening.⁸⁶ The same or similar phenomenon almost certainly exists in adults.⁸⁷ Changes in the microbiome could also contribute to exacerbations; changes occur in the microbiome as a consequence of antibiotic exposure, and after removal of the antibiotic exposure the microbiome can return to its previous state or remain altered (for better or for worse). Additionally, there might be interactions between species that could influence their virulence and pathogenicity.⁸⁸ Study results of microbiome changes have been inconsistent and could be more related to the individuals studied or to the differences in the treatments used. Indeed, one study found very little change in composition of the microbiome over time despite antibiotic treatment and exacerbations.⁸² A long-term study of macrolide antibiotics (the BLESS study) showed a decreased overall diversity of the microbiome and increase in the relative abundance of *Pseudomonas* as a result of the reduced relative abundance of other organisms sensitive to macrolides.⁸⁹ The clinical relevance of this observation is

not known, but was not associated with an increase in clinically relevant *P aeruginosa* infections. However, the findings suggest that antibiotic treatment could contribute to potentially pathogenic changes in the microbiota in some cases.

Although bacteria have received the most attention in microbiome studies, fungi and mycobacteria are also important in bronchiectasis. *A fumigatus* has been isolated in patients with advanced disease and in individuals with allergic bronchopulmonary aspergillosis. *Aspergillus* is the taxa that most greatly differs between healthy individuals and patients with bronchiectasis and its abundance has been associated with exacerbations, suggesting that *Aspergillus* could be an important contributor to airway inflammation in some patients.⁹⁰ By contrast, *Candida albicans* has less clinical significance. It is also frequently isolated, and although some studies suggest a higher frequency of exacerbations in patients with *Candida* in sputum cultures, this finding could reflect reverse causation as *Candida* might be isolated after antibacterial treatment as a result of disturbance of bacterial microbiota.

Most studies to date are inherently limited by the biases of research methods in that these microbiota studies do not adequately detect mycobacteria,⁹¹ do not detect fungi or viruses, and underestimate amounts of some typical bacteria such as *Staphylococcus*. Emerging approaches such as metagenomics allow comprehensive detection of bacterial, viral, and fungal populations simultaneously, while also potentially providing data for the carriage of virulence genes and genes associated with antimicrobial resistance.⁹² Cost, technical, and bioinformatics limitations are gradually being overcome to allow these studies to be done more widely.

Conclusion

Ultimately, clinical variables can only provide modest predictive accuracy for bronchiectasis outcomes and provide little information about the underlying biology of the disease. Recent progress in understanding genotypes and endotypes, the process of defining groups of patients by pathobiology often with use of biomarkers, is at an early stage in bronchiectasis but offers promising approaches to develop therapeutic interventions for some patients with bronchiectasis. Hopefully, in the near future a standardised approach to the evaluation of patients with bronchiectasis will exist, and will use genetic analyses and local and systemic biomarkers to stratify patients in terms of prognosis and therapy.

Contributors

All authors contributed to the planning, writing, and editing of the manuscript. All authors reviewed the final manuscript and are in agreement with regard to the contents.

Declaration of interests

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