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

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Abstract

Bronchiectasis is a condition characterized by pathological dilation of the airways. More specifically, the radiographic demonstration of airways enlargement is the common feature of a heterogeneous set of conditions and clinical presentations. There are no approved therapies for the condition other than for bronchiectasis caused by cystic fibrosis. The heterogeneity of bronchiectasis is the major challenge in clinical practice and the major reason for difficulty in achieving endpoints in clinical trials. Recent observations have improved our knowledge regarding bronchiectasis such that it may be more effective to describe patients according to a heterogeneous group of endotypes, defined by a distinct functional or pathobiological mechanism, or clinical phenotypes, defined by relevant and common features of disease. In doing so, we may finally develop more specific therapies needed to effectively treat our patients. Here we describe some of the recent advances in endotyping, genetics and disease heterogeneity of bronchiectasis including observations related to the microbiome.

Bronchiectasis is defined as permanent enlargement of the airways [1], a condition with its own ICD-10 CM diagnostic code (i.e. J47.9) and mostly the result of an intrinsic airways pathology resulting in dilation. There are multiple etiologies of bronchiectasis and a broad array of clinical presentations.[2] The extent of bronchiectasis can range from focal disease, limited to one segment or lobe, to diffuse disease, involving both lungs in all lobes. The bronchiectatic findings range from subtle dilation to cystic changes in the airways. Some patients will be asymptomatic and the bronchiectasis is discovered unexpectedly while others suffer daily symptoms of cough and sputum production with periodic worsening of their symptoms known as exacerbations.[3] The diagnosis of bronchiectasis is increasing worldwide. Previously classified as a rare or orphan disease, bronchiectasis has now been reported at rates up to 566 per 100,000 population with a prevalence that has increased 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 United States or Europe for this indication. The exception is the bronchiectasis due to cystic fibrosis (CF), for which there are several approved medications, but none have had their label expanded to include other causes of bronchiectasis.[5] Yet there are guidelines that recommend treatments for bronchiectasis[5], and reports of therapies have been demonstrated to associate with clinical benefit [6, 7], suggesting that only some patients with bronchiectasis are likely to benefit from those therapies.[8, 9] The pathway to more precise treatment will require a greater understanding of our patients beyond a mere imaging study. What follows is a review of recent studies that have attempted to better describe patients according to a heterogeneous group of endotypes, defined by a distinct functional or pathobiological mechanism[10], or clinical phenotypes, defined by relevant and common features of disease.[11] It is hoped that this approach to better understand our patients with bronchiectasis may finally provide us with the knowledge needed to more effectively treat them.

Pathophysiology of disease

The list of conditions known to cause or be associated with bronchiectasis is long but most can be found to have common features leading to the remodeling of the airways and dilation. A useful pathophysiologic pathway has been described as a cycle of events promoting impaired mucociliary clearance and retention of airways secretions that disrupt the normal host defenses and render the airways more vulnerable to establishment of chronic infection. The persistence of bacterial pathogens incites an inflammatory response that results in injury and abnormal remodeling 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 many conditions enter into the cycle; CF and primary ciliary dyskinesia (PCD) have impaired mucociliary clearance; immunodeficiency can result in recurrent and persistent infection; injury to the airways, either because of severe infection or mechanical injury (e.g. toxic inhalation or chronic aspiration) can result in an impaired healing of the airways, and so on. However, interactions are far more complex, each pathophysiologic step contributing to all others perhaps better described as a vortex (Figure 1).

How this pathophysiologic model results in dilation of the airways and why there is such heterogeneity in extent of disease are less well understood. A simple explanation is that impaired mucociliary function results in an accumulation of material that obstructs and stents the airway while remodeling occurs. Another hypothesis can be found in the study of polycystic kidney disease (PKD) in which a non-motile ciliary abnormality in renal epithelial cells results in cellular hypertrophy and hyperplasia, and cyst formation.[12] Since patients with PKD also have bronchiectasis[13], this suggests there may be a link between cilia, cellular signaling processes, and bronchiectasis. An animal ciliary knockout model of PKD demonstrated loss of airway motile cilia as well as bronchial remodeling in the absence of inflammation but with proliferation of facultative progenitor cells.[14] Such a role for ciliary function may offer a commonality among the varied etiologies of bronchiectasis.

The radiographic features help to explain why some patients will have focal disease (e.g. because of severe injury) rather than diffuse (e.g. PCD), or why some have disease in the lower lobes (e.g. recurrent aspiration). While some diagnoses have easily available and interpretable diagnostic testing (e.g. CF), others are less easily established, and yet this may still not be sufficient in defining which patients are likely to respond to specific therapies. Alternative characteristics (e.g. genotyping or biomarkers) may better characterize patients to understand how best to develop and use therapies.

Endotypes and genotypes

While the largest group of patients will have the diagnosis of idiopathic bronchiectasis for lack of a specific etiology, reviewing those conditions with well-known, genetics-based pathways offers insights into understanding the underlying mechanisms of bronchiectasis pathogenesis and development of specific treatment regimens. However, the interaction 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, while classification based on inflammatory endotypes can correlate with effective, specific anti-inflammatory therapies. [15]

Cystic Fibrosis (CF)

CF serves as the prime example of how disease categorization based on genotype can drive effective therapeutic intervention. CF is primarily a disorder of mucociliary clearance caused by altered epithelial ion transport. There are well characterized biomarkers, such as sweat chloride and transepithelial potential difference assays, that have been useful in the diagnosis and research assessment of therapeutic response. Discovery of the causative gene for CF in 1989 led to increasing knowledge of the protein product, cystic fibrosis transmembrane conductance regulator (CFTR), including its structure, function, and the protein synthesis pathway from nucleus to insertion and proper functioning in the epithelial apical membrane. [16, 17] The correlation between specific genetic mutations and their impact on CFTR quantity and function has led to remarkable genotype-specific treatment (https://www.cff.org/Trials/Pipeline) that can significantly improve the clinical course of bronchiectasis and other manifestations of disease (Figure 2). While the airway dilation may remain, airway inflammation, secretion clearance, and control of infection can all improve with CFTR modulator therapy. [18, 19]

Primary Ciliary Dyskinesia (PCD)

PCD is another genetic disorder of mucociliary clearance characterized by disordered function of motile cilia. Bedside measurement of nitric oxide (NO) production is a useful biomarker of ciliary motility, [20] but it must be emphasized that PCD genotypes associated with normal nasal NO have been described. [21] Measurement of nasal NO production and high-speed video assessment of ciliary beat characteristics may be useful markers of drug efficacy in future clinical trials. [22] In contrast to the monogenic etiology of CF, the assembly and regulation of ciliary proteins is under the control of multiple genes. [23] While 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 PCD advances, this genotype/structure-function relationship may prove useful for drug targeting similar to the path that CFTR modulator therapeutics development has taken in CF.

Immune Deficiencies

Bronchiectasis is a common manifestation of many primary immune deficiencies (PID) and disorders of immune regulation. These conditions can be subdivided based roughly on the primary immune cells of origin. Biomarkers that can be useful in diagnosis and assessment of treatment include lymphocyte phenotyping with delineation of T, B, and NK cell numbers, quantitative immunoglobulin levels, 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 PID-associated causes of bronchiectasis. [24] While abnormally low immunoglobulin levels may 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 immunodeficiency characterized by significant reductions in IgG and IgA or IgM and presentation later in life with recurrent pyogenic sinopulmonary infections, is clinically and genetically a heterogeneous disorder. [25] X-linked agammaglobulinemia (XLA) is caused by mutations in the Bruton tyrosine kinase (*BTK*) gene and can result in a profound humoral immunodeficiency. [26] However, even XLA can have a variable clinical phenotype based on genotype with adults having a higher proportion of splice-site mutations and lower proportion of frameshift mutations than children with XLA. [27] The autosomal dominant hyperimmunoglobulin E syndrome (AD-HIES or Job's syndrome) is another example of a rare PID that may be identified by its characteristic markedly elevated IgE levels and clinical findings of eczema, recurrent skin and pulmonary infections, skeletal abnormalities and coarse facial features. However, with this disease, the high IgE 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. [28] STAT3 is important for several key airway defense mechanisms including TH17-based cytokine signaling leading to upregulation of antimicrobial peptides. It is also felt to play a role in proper remodeling after epithelial injury by directing differentiation of airway basal cells into ciliated cells and away from mucus secreting epithelial cells. [29] Mutations in *STAT3* affecting these pathways likely account for the high prevalence of bronchiectasis and cystic changes (pneumatoceles) seen in this disease. With the widespread availability of whole exome sequencing, it is likely that mutations in genes affecting immune function and regulation can account for unsuspected underlying systemic immune causes for patients with recurring respiratory tract infections leading to bronchiectasis with atypical late presentations and diagnosed in adulthood. [30, 31]

Autoimmune Diseases

Several autoimmune diseases, most notably rheumatoid arthritis and inflammatory bowel disease, have been 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; they are not so helpful in characterizing the associated airway disease. While infections may be common in bronchiectasis associated with these disorders, frequently the inflammatory component predominates. In the case of ulcerative colitis associated bronchiectasis, the airway findings of cobblestoning, ulcerations and mucosal lymphoplasmocytic infiltration can mimic bowel findings. These pulmonary manifestations may respond to anti-inflammatory agents such as inhaled or systemic steroids; however, some cases may require tumor necrosis factor alpha blockade (once infection is identified and controlled with antibiotics) or other immunodulatory drugs commonly used to treat bowel inflammation to control the progression of bronchiectasis. [32] Causative genes have not been identified for these disorders. For inflammatory bowel disease, associated genetic risk loci have been reported including *CARD15/NOD2*, *ATG16L1*, *IRGM*, *IL23R*, *TNFSF15,* and *HLAD-QA1*. Additional work is needed to know whether these correlate with airway manifestations and can lead to more specific therapeutic interventions. [33]

Allergic Bronchopulmonary Aspergillosis (ABPA)

ABPA represents a unique overlap between immune dysregulation and obstructive airway diseases such as asthma and CF. While it is associated with filamentous fungi in the airway, biomarkers of the allergic inflammatory response such as eosinophilia, total IgE, serum precipitans, and Aspergillus-specific IgE with IgG as a marker of *A. fumigatus* exposure are prominent in the diagnostic criteria. [34, 35] The bronchiectasis frequently is proximal and may have an exaggerated saccular, plugged appearance. A recent study comparing ABPA patients to atopic asthmatics and healthy controls, identified ABPA-associated SNPs in TLR3, IL4R, and IL13. [36]

These and other reported potential genetic susceptibility loci may be helpful in elucidating pathways and pointing to more specific therapies.

COPD and Asthma

The general relationship between asthma, COPD, and bronchiectasis remains unclear as to directionality of development. [37] Bronchiectasis can be seen in the setting of both asthma and COPD and has been associated with more advanced stages of these diseases.[38, 39] Conversely as bronchiectasis progresses, increasing degrees of chronic airway obstruction can be seen and labeled as COPD and some patients with bronchiectasis may have eosinophilia, elevated IgE, and at least partially reversible airway obstruction suggesting an asthmatic component to their disease. Bronchiectasis has been historically under-recognized and so at least some of the overlap represents historic misdiagnosis. Endotyping to guide therapy has garnered much attention in asthma management and biomarkers (e.g. eosinophilia or increased IgE) may be useful in identifying patients with bronchiectasis who may benefit from directed anti-inflammatory treatment. The prime example of genetic overlap between COPD and bronchiectasis is alpha-1 antitrypsin deficiency in which there is a correlation between the biomarker of alpha-1 antitrypsin level, the genotype and disease severity.

Idiopathic Bronchiectasis associated with 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 nontuberculous mycobacteria (NTM). [40] This group of patients are reported as predominantly post-menopausal, nonsmoking women with no known predisposing factors who present with chronic cough. [41]

They share characteristics with other endotypes, notably a high prevalence of CFTR mutations and evidence of ciliary dysfunction, [22, 42, 43] but they do not meet diagnostic criteria for CF or PCD. Such observations suggest the etiology of the condition is likely to be multifactorial in which mucociliary clearance defects may play a key role.

These patients have physical characteristics such as a tall, asthenic morphotype, scoliosis, pectus excavatum, mitral valve prolapse, and dural ectasia that overlap with heritable connective tissue disorders such as Marfan and Ehlers Danlos syndromes. [43, 44] Both bronchiectasis and pulmonary NTM infections have been noted in a well characterized population of these heritable connective tissue disorders. [45] Conversely, key characteristics such as bronchiectasis, NTM infection, and connective tissue disease features have been reported in a high proportion of 1st and 2nd degree relatives of carefully phenotyped idiopathic bronchiectasis patients with pulmonary NTM infections, strongly suggesting a genetic component to the disease. [45] Whole exome sequencing, using a candidate gene analysis of low frequency, potentially protein-altering variants, identified a significantly higher prevalence of variants in connective tissue disease associated genes and in mucociliary clearance associated (CFTR and cilia related) genes in NTM-affected probands and NTM-affected and unaffected family members compared to a healthy control reference population. [46] Many of the NTM-unaffected family members had bronchiectasis and/or connective tissue disease traits. A higher prevalence of variants in genes related to systemic mycobacterial control distinguished those 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 NO, ciliary beat frequency), and genetic analysis, it may be possible to fit patients with idiopathic bronchiectasis into key endotypes that may 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, ciliary beating characteristics, mitigate vascular and other sequelae of connective tissue disorders, or enhance relevant systemic immune pathways may alter host susceptibility and improve the disease course in patients with idiopathic bronchiectasis and chronic NTM infections (Figure 4).

Disease heterogeneity beyond etiology: clinical phenotypes

Evaluating patients with bronchiectasis requires knowledge of the heterogeneity of clinical presentation and variable clinical course. Patients with apparently mild symptoms at presentation may still have adverse prognostic factors and experience rapid progression of disease, while others with seemingly severe symptoms at the outset may be easily managed and with a good prognosis.[47] A multidimensional approach to patient assessment will incorporate clinical history, physical examination, appropriate laboratory testing, microbiology and functional assessments. Some etiologies of bronchiectasis have specific clinical presentations or have characteristics that can suggest the underlying etiological diagnosis (Table 1) and inform use of diagnostic testing.[48-50] However, many of these features remain non-specific and so efforts have been made to identify clinically recognizable sets of observable characteristics that link to clinical outcomes (i.e. clinical phenotypes).[51]

Exacerbations of bronchiectasis, defined clinically as worsening of the usual respiratory symptoms [52], are significant events in the natural history of bronchiectasis. Patients with ≥3 exacerbations per year had worse health status, were more likely to be hospitalized, and had increased mortality.[53] Most importantly, the frequent exacerbator was identified as a true phenotype since the majority of patients consistently suffered exacerbations over time, while patients who did not have a history of exacerbations rarely had events during follow-up. As has been shown for COPD [54] and CF [55], a past history of exacerbations in patients with bronchiectasis is the strongest predictor of future events while individual co-morbidities, bacteriology, severity of radiological disease and other parameters explained only a very small amount of the variance in exacerbation rate.[53] This suggests that we do not yet understand what leads a patient to be a frequent exacerbator and so in clinical practice the history of exacerbations is the only parameter we can confidently use for future prediction.

Various studies have attempted to use statistical clustering techniques to identify subgroups of bronchiectasis patients with different characteristics.[56, 57] Most clusters identified have been based on current age, age of onset of disease, and severity, and all have failed to replicate in independent cohorts suggesting they are not true phenotypes. The major phenotype that has been identified in all cohorts is patients chronically infected with *P. aeruginosa*. Patients with chronic infection by *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.[58-60] *P. aeruginosa* can exhibit adaptive behaviors allowing it to survive in a hostile environment such as the human airways; the production of biofilms obstructs exposure of bacteria to antibiotics and phagocytes.[61, 62] *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.[63] However, the mere presence of *P. aeruginosa* has not been sufficient to define those patients who benefit from aerosolized suppressive antibiotic therapy[8]; since there are patients who do benefit from inhaled antibiotics[6], this suggests there may be other factors (e.g. bacterial abundance) that are more predictive.

There are patients who have “dry bronchiectasis”, in that they do not produce daily sputum, a syndrome long recognized; a case series published in the British Medical Journal in 1933 describes 20 cases arising from infections in childhood where bronchiectasis was associated with cough and occasional hemoptysis without prominent sputum production. [64] Such patients have lower symptom scores but surprisingly have a higher mortality rate than patients who have chronic infection or daily sputum.[56] Dry bronchiectasis has been classically associated with non-tuberculous mycobacterial (NTM) infection.

In contrast, there is a group of patients who present with excessive sputum production but without the consistent finding of bacteria in sputum cultures. Such patients have been described as having “sterile bronchorrhea” although modern molecular microbiology techniques teach us that sputum samples are never sterile.[65] This group has been classically associated with inflammatory bowel disease where sputum samples contain neutrophils and necrotic material but do not have detectable pathogens.[66] Further research is required to identify other meaningful clinical phenotypes that are independent of etiology.

Microbiology and the microbiome

Chronic bacterial infection is a characteristic feature of many patients with bronchiectasis. The term chronic infection is preferred to colonization as the latter 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 certain organisms have prognostic implications; this information can help guide treatment of exacerbations and may identify patients for whom long term suppressive antibiotic therapy may be effective.[67] Traditional culture methods for bacteria show that nearly 80% of patients will regularly grow pathogens in sputum samples, the most frequent being *Pseudomonas aeruginosa* and *Haemophilus influenzae* but other Gram-negative (e.g. *Moraxella catarrhalis, Escherichia sp.* and *Klebsiella sp*) and Gram-positive (e.g. *Streptococcus pneumoniae* and *Staphylococcus aureus*) organisms are isolated with frequency.[68] Whereas *H. influenzae* and *P. aeruginosa* are the most common organisms in European studies, the US bronchiectasis registry reported high rates of isolation of NTM (50%) and *P. aeruginosa* (33%), while *H. influenzae* was relatively uncommon (8%).[69] The reason for the higher frequency of NTM in the United States is not clear, but may reflect some element of selection bias as many US registry sites are also referral centers for NTM lung disease. [69]

Our 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 (a.k.a. the microbiome). A microbiome analysis of healthy airways reveals a rich, diverse community of bacteria that are present in low abundance.[70] It is premature to define a normal airways flora, as some (or all) of these could represent transient populations introduced through microaspiration. Across a number of respiratory diseases it has been demonstrated that disease is associated with a loss of diversity, through the loss of important bacterial taxa, or by the dominance of a single or small group of taxa.[71] The latter is referred to as a loss of evenness of the microbiota while the former 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 been associated with lower lung function in bronchiectasis [72], although it cannot be stated whether this is causal or the result of 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 bronchiectasis[73] and have been associated with more neutrophil mediated inflammation and exacerbations.[71] However, there is a subgroup of patients with microbiota dominated with firmicutes (e.g. the anaerobe *Veillonella*) that have frequent exacerbations despite lower levels of neutrophilic inflammation.[74-76]

There is still much to learn about microbiota changes relevant to the development of bronchiectasis as well as its progression. The importance of early persistent bacterial infection in CF and PCD is well established, but there is increased interest in persistent bacterial bronchitis in children that could lead to development of bronchiectasis, suggesting that aggressive treatment with antibiotis could ultimately prevent this from happening.[77] Changes in the microbiome could also contribute to an exacerbation, there are changes in the microbiome as a consequence of antibiotic exposure, and after removal of the antibiotic exposure the microbiome can return to the prior state or remain altered (for better or for worse). In addition, there may be species interactions that may influence their virulence and pathogenicity.[78] Studies of microbiome changes have been inconsistent and may be more related to the individual. Indeed, one study found very little change in composition of the microbiome over time despite antibiotic treatment and exacerbations.[73] A long-term study of macrolide antibiotics (BLESS) demonstrated 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. [79] The clinical relevance of this observation is not known, but this was not associated with an increase in clinically relevant *P. aeruginosa* infections. However, it suggests that antibiotic treatment may contribute to potentially pathogenic changes in the microbiota in some cases.

While bacteria have received the most attention in microbiome studies, fungi and mycobacteria are also important in bronchiectasis. *Aspergillus fumigatus* is isolated in patients with advanced disease and in individuals with ABPA. *Aspergillus* is the main different taxa between healthy controls and bronchiectasis patients and its abundance has been associated with exacerbations, suggesting that *Aspergillus* may be an important contributor to airway inflammation in some patients.[80] In contrast the clinical significance of *Candida albicans* is less worrisome. It, too, is frequently isolated, and although some studies suggest a higher frequency of exacerbations in patients with *Candida* in sputum cultures, this may reflect reverse causation as *Candida* may be isolated after antibacterial treatment as a result of disturbance of bacterial microbiota.

The majority of studies to date are inherently limited by the biases of current methodologies in that these microbiota studies do not adequately detect mycobacteria[81], do not detect fungi or viruses, and underestimate some typical bacteria such as *Staphylococci*. Emerging metagenomics approaches allow comprehensive detection of bacterial, viral and fungal populations simultaneously, while also potentially providing data on the carriage of virulence genes and genes associated with antimicrobial resistance.[82] Cost, technical and bioinformatics limitations are gradually being overcome to allow these studies to be performed more widely.

Conclusions

Ultimately clinical variables can only provide modest predictive accuracy for bronchiectasis outcomes and tell us nothing about the underlying biology of the disease. Recent progress in understanding genotypes and endotypes, the process of defining groups of patients by pathobiology often using biomarkers, is at an early stage in bronchiectasis but offer promising approaches to develop therapeutic interventions for some patients with bronchiectasis. Hopefully, in the near future we will have a standardized approach to the evaluation of patients with bronchiectasis, and will use genetic analyses and local and systemic biomarkers to stratify patients in terms of prognosis and therapy.

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Conflict of Interest Statement

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References

1. Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. The European respiratory journal. 2015; **45**(5): 1446-62.
2. Araujo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon T, et al. Standardised classification of the aetiology of bronchiectasis using an objective algorithm. The European respiratory journal. 2017; **50**(6): 1701289.
3. Spinou A, Siegert RJ, Guan WJ, Patel AS, Gosker HR, Lee KK, et al. The development and validation of the Bronchiectasis Health Questionnaire. The European respiratory journal. 2017; **49**(5): 1601532.
4. Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. The European respiratory journal. 2016; **47**(1): 186-93.
5. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. The European respiratory journal. 2017; **50**(3): 1700629.
6. Nadig TR, Flume PA. Aerosolized Antibiotics for Patients with Bronchiectasis. Am J Respir Crit Care Med. 2016; **193**(7): 808-10.
7. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA. 2013; **309**(12): 1260-7.
8. Aksamit T, De Soyza A, Bandel TJ, Criollo M, Elborn JS, Operschall E, et al. RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. The European respiratory journal. 2018; **51**(1): 1702053.
9. De Soyza A, Aksamit T, Bandel TJ, Criollo M, Elborn JS, Operschall E, et al. RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. The European respiratory journal. 2018; **51**(1): 1702052.
10. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet. 2008; **372**(9643): 1107-19.
11. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010; **182**(5): 598-604.
12. Chapin HC, Caplan MJ. The cell biology of polycystic kidney disease. The Journal of cell biology. 2010; **191**(4): 701-10.
13. Driscoll JA, Bhalla S, Liapis H, Ibricevic A, Brody SL. Autosomal dominant polycystic kidney disease is associated with an increased prevalence of radiographic bronchiectasis. Chest. 2008; **133**(5): 1181-8.
14. Gilley SK, Stenbit AE, Pasek RC, Sas KM, Steele SL, Amria M, et al. Deletion of airway cilia results in noninflammatory bronchiectasis and hyperreactive airways. Am J Physiol Lung Cell Mol Physiol. 2014; **306**(2): L162-9.
15. Svenningsen S, Nair P. Asthma Endotypes and an Overview of Targeted Therapy for Asthma. Front Med (Lausanne). 2017; **4**: 1-10.
16. Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science. 1989; **245**(4922): 1059-65.
17. Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. Cell. 1993; **73**(7): 1251-4.
18. Sheikh SI, Long FR, McCoy KS, Johnson T, Ryan-Wenger NA, Hayes D, Jr. Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation. J Cyst Fibros. 2015; **14**(1): 84-9.

19. Heltshe SL, Mayer-Hamblett N, Burns JL, Khan U, Baines A, Ramsey BW, et al. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015; **60**(5): 703-12.
20. Shapiro AJ, Josephson M, Rosenfeld M, Yilmaz O, Davis SD, Polineni D, et al. Accuracy of Nasal Nitric Oxide Measurement as a Diagnostic Test for Primary Ciliary Dyskinesia. A Systematic Review and Meta-analysis. Annals of the American Thoracic Society. 2017; **14**(7): 1184-96.
21. Shoemark A, Moya E, Hirst RA, Patel MP, Robson EA, Hayward J, et al. High prevalence of CCDC103 p.His154Pro mutation causing primary ciliary dyskinesia disrupts protein oligomerisation and is associated with normal diagnostic investigations. Thorax. 2018; **73**(2): 157-66.
22. Fowler CJ, Olivier KN, Leung JM, Smith CC, Huth AG, Root H, et al. Abnormal nasal nitric oxide production, ciliary beat frequency, and Toll-like receptor response in pulmonary nontuberculous mycobacterial disease epithelium. Am J Respir Crit Care Med. 2013; **187**(12): 1374-81.
23. Horani A, Ferkol TW, Dutcher SK, Brody SL. Genetics and biology of primary ciliary dyskinesia. Paediatric respiratory reviews. 2016; **18**: 18-24.
24. Buckley RH. Pulmonary complications of primary immunodeficiencies. Paediatric respiratory reviews. 2004; **5 Suppl A**: S225-33.
25. Ameratunga R, Lehnert K, Woon ST, Gillis D, Bryant VL, Slade CA, et al. Review: Diagnosing Common Variable Immunodeficiency Disorder in the Era of Genome Sequencing. Clinical reviews in allergy & immunology. 2018; **54**(2): 261-8.
26. Vetrie D, Vorechovsky I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature. 1993; **361**(6409): 226-33.
27. Broides A, Yang W, Conley ME. Genotype/phenotype correlations in X-linked agammaglobulinemia. Clin Immunol. 2006; **118**(2-3): 195-200.
28. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007; **357**(16): 1608-19.
29. Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, et al. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. J Exp Med. 2009; **206**(6): 1291-301.
30. Hsu AP, Pittaluga S, Martinez B, Rump AP, Raffeld M, Uzel G, et al. IL2RG reversion event in a common lymphoid progenitor leads to delayed diagnosis and milder phenotype. J Clin Immunol. 2015; **35**(5): 449-53.
31. Coulter TI, Chandra A, Bacon CM, Babar J, Curtis J, Screaton N, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase delta syndrome: A large patient cohort study. The Journal of allergy and clinical immunology. 2017; **139**(2): 597-606 e4.
32. Egan JP, 3rd, Seides BJ, Olivier KN, Addrizzo-Harris D. Successful treatment of ulcerative bronchiolitis in a woman with refractory Mycobacterium intracellulare infection. BMJ Case Rep. 2015; **2015**: bcr2015209604.
33. Ye BD, McGovern DP. Genetic variation in IBD: progress, clues to pathogenesis and possible clinical utility. Expert Rev Clin Immunol. 2016; **12**(10): 1091-107.
34. Agarwal R, Aggarwal AN, Dhooria S, Singh Sehgal I, Garg M, Saikia B, et al. A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. The European respiratory journal. 2016; **47**(2): 490-8.
35. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy. 2013; **43**(8): 850-73.

36. Overton NL, Denning DW, Bowyer P, Simpson A. Genetic susceptibility to allergic bronchopulmonary aspergillosis in asthma: a genetic association study. Allergy Asthma Clin Immunol. 2016; **12**: 47.
37. Blasi F, Chalmers JD, Aliberti S. COPD and bronchiectasis: phenotype, endotype or co-morbidity? COPD. 2014; **11**(6): 603-4.
38. Hurst JR, Elborn JS, De Soyza A. COPD-bronchiectasis overlap syndrome. The European respiratory journal. 2015; **45**(2): 310-3.
39. Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. The European respiratory journal. 2016; **47**(6): 1680-6.
40. Prince DS, Peterson DD, Steiner RM, Gottlieb JE, Scott R, Israel HL, et al. Infection with Mycobacterium avium complex in patients without predisposing conditions. N Engl J Med. 1989; **321**(13): 863-8.
41. Reich JM, Johnson RE. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. Chest. 1992; **101**(6): 1605-9.
42. Ziedalski TM, Kao PN, Henig NR, Jacobs SS, Ruoss SJ. Prospective analysis of cystic fibrosis transmembrane regulator mutations in adults with bronchiectasis or pulmonary nontuberculous mycobacterial infection. Chest. 2006; **130**(4): 995-1002.
43. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med. 2008; **178**(10): 1066-74.
44. Daniels ML, Birchard KR, Lowe JR, Patrone MV, Noone PG, Knowles MR. Enlarged Dural Sac in Idiopathic Bronchiectasis Implicates Heritable Connective Tissue Gene Variants. Annals of the American Thoracic Society. 2016; **13**(10): 1712-20.
45. Leung JM, Olivier KN, Prevots DR, McDonnell NB. Beyond Marfan: the clinical impact of bronchiectasis and non-tuberculous mycobacteria in connective tissue diseases. Int J Tuberc Lung Dis. 2015; **19**(11): 1409.
46. Szymanski EP, Leung JM, Fowler CJ, Haney C, Hsu AP, Chen F, et al. Pulmonary Nontuberculous Mycobacterial Infection. A Multisystem, Multigenic Disease. Am J Respir Crit Care Med. 2015; **192**(5): 618-28.
47. McDonnell MJ, Aliberti S, Goeminne PC, Dimakou K, Zucchetti SC, Davidson J, et al. Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. Thorax. 2016; **71**(12): 1110-1118.
48. Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soyza A, et al. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. Annals of the American Thoracic Society. 2015; **12**(12): 1764-70.
49. Shoemark A, Ozerovitch L, Wilson R. Aetiology in adult patients with bronchiectasis. Respiratory medicine. 2007; **101**(6): 1163-70.
50. McShane PJ, Naureckas ET, Strek ME. Bronchiectasis in a diverse US population: effects of ethnicity on etiology and sputum culture. Chest. 2012; **142**(1): 159-67.
51. Chalmers JD, Chotirmall SH. New therapies and new perspectives. Lancet Respir Med. 2018; **in press**.
52. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. The European respiratory journal. 2017; **49**(6).
53. Chalmers JD, Aliberti S, Filonenko A, Shteinberg M, Goeminne PC, Hill AT, et al. Characterisation of the "Frequent Exacerbator Phenotype" in Bronchiectasis. Am J Respir Crit Care Med. 2018; **197**(11): 1410-1420.

54. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010; **363**(12): 1128-38.

55. VanDevanter DR, Morris NJ, Konstan MW. IV-treated pulmonary exacerbations in the prior year: An important independent risk factor for future pulmonary exacerbation in cystic fibrosis. J Cyst Fibros. 2016; **15**(3): 372-9.

56. Aliberti S, Lonni S, Dore S, McDonnell MJ, Goeminne PC, Dimakou K, et al. Clinical phenotypes in adult patients with bronchiectasis. The European respiratory journal. 2016; **47**(4): 1113-22.

57. Guan WJ, Jiang M, Gao YH, Li HM, Xu G, Zheng JP, et al. Unsupervised learning technique identifies bronchiectasis phenotypes with distinct clinical characteristics. Int J Tuberc Lung Dis. 2016; **20**(3): 402-10.

58. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis. Annals of the American Thoracic Society. 2015; **12**(11): 1602-11.

59. Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. The European respiratory journal. 2009; **34**(4): 843-9.

60. Araujo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon TC, et al. The independent contribution of Pseudomonas aeruginosa infection to long-term clinical outcomes in bronchiectasis. The European respiratory journal. 2018; **51**(2).

61. Hilliam Y, Moore MP, Lamont IL, Bilton D, Haworth CS, Foweraker J, et al. Pseudomonas aeruginosa adaptation and diversification in the non-cystic fibrosis bronchiectasis lung. The European respiratory journal. 2017; **49**(4).

62. Frija-Masson J, Martin C, Regard L, Lothe MN, Touqui L, Durand A, et al. Bacteria-driven peribronchial lymphoid neogenesis in bronchiectasis and cystic fibrosis. The European respiratory journal. 2017; **49**(4).

63. Nair C, Shoemark A, Chan M, Ollosson S, Dixon M, Hogg C, et al. Cyanide levels found in infected cystic fibrosis sputum inhibit airway ciliary function. The European respiratory journal. 2014; **44**(5): 1253-61.

64. Wall C, Hoyle JC. Observations on DRY BRONCHIECTASIS. Br Med J. 1933; **1**(3770): 597-620.

65. Smith DJ. Phenotyping bronchiectasis: is it all about sputum and infection? The European respiratory journal. 2016; **47**(4): 1037-9.

66. Camus P, Colby TV. Bronchiectasis associated with inflammatory bowel disease. Eur Respir Mon. 2011; **52**: 163-77.

67. Vallieres E, Tumelty K, Tunney MM, Hannah R, Hewitt O, Elborn JS, et al. Efficacy of Pseudomonas aeruginosa eradication regimens in bronchiectasis. The European respiratory journal. 2017; **49**(4).

68. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med. 2014; **189**(5): 576-85.

69. Aksamit TR, O'Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels MLA, et al. Adult Patients With Bronchiectasis: A First Look at the US Bronchiectasis Research Registry. Chest. 2017; **151**(5): 982-92.

70. Faner R, Sibila O, Agusti A, Bernasconi E, Chalmers JD, Huffnagle GB, et al. The microbiome in respiratory medicine: current challenges and future perspectives. The European respiratory journal. 2017; **49**(4).

71. Tunney MM, Einarsson GG, Wei L, Drain M, Klem ER, Cardwell C, et al. Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. Am J Respir Crit Care Med. 2013; **187**(10): 1118-26.

72. Rogers GB, van der Gast CJ, Cuthbertson L, Thomson SK, Bruce KD, Martin ML, et al. Clinical measures of disease in adult non-CF bronchiectasis correlate with airway microbiota composition. Thorax. 2013; **68**(8): 731-7.

73. Cox MJ, Turek EM, Hennessy C, Mirza GK, James PL, Coleman M, et al. Longitudinal assessment of sputum microbiome by sequencing of the 16S rRNA gene in non-cystic fibrosis bronchiectasis patients. PloS one. 2017; **12**(2): e0170622.

74. Chalmers JD, Moffitt KL, Suarez-Cuartin G, Sibila O, Finch S, Furrie E, et al. Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis. Am J Respir Crit Care Med. 2017; **195**(10): 1384-93.

75. Taylor SL, Rogers GB, Chen AC, Burr LD, McGuckin MA, Serisier DJ. Matrix metalloproteinases vary with airway microbiota composition and lung function in non-cystic fibrosis bronchiectasis. Annals of the American Thoracic Society. 2015; **12**(5): 701-7.

76. Rogers GB, Zain NM, Bruce KD, Burr LD, Chen AC, Rivett DW, et al. A novel microbiota stratification system predicts future exacerbations in bronchiectasis. Annals of the American Thoracic Society. 2014; **11**(4): 496-503.

77. Ishak A, Everard ML. Persistent and Recurrent Bacterial Bronchitis-A Paradigm Shift in Our Understanding of Chronic Respiratory Disease. Frontiers in pediatrics. 2017; **5**: 1-9.

78. Hughes DT, Sperandio V. Inter-kingdom signalling: communication between bacteria and their hosts. Nature reviews Microbiology. 2008; **6**(2): 111-20.

79. Rogers GB, Bruce KD, Martin ML, Burr LD, Serisier DJ. The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fibrosis bronchiectasis: an analysis from the randomised, double-blind, placebo-controlled BLESS trial. Lancet Respir Med. 2014; **2**(12): 988-96.

80. Mac Aogain M, Chandrasekaran R, Lim Yick Hou A, Teck Boon L, Liang Tan G, Hassan T, et al. Immunological Corollary of the Pulmonary Mycobiome in Bronchiectasis: The Cameb Study. The European respiratory journal. 2018.

81. Caverly LJ, Carmody LA, Haig SJ, Kotlarz N, Kalikin LM, Raskin L, et al. Culture-Independent Identification of Nontuberculous Mycobacteria in Cystic Fibrosis Respiratory Samples. PloS one. 2016; **11**(4): e0153876.

82. Aliberti S, Masefield S, Polverino E, De Soyza A, Loebinger MR, Menendez R, et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. The European respiratory journal. 2016; **48**(3): 632-47.

83. Lopes-Pacheco M. CFTR Modulators: Shedding Light on Precision Medicine for Cystic Fibrosis. Front Pharmacol. 2016; **7**: 275.

84. Horani A, Ferkol TW. Primary ciliary dyskinesia and associated sensory ciliopathies. Expert Rev Respir Med. 2016; **10**(5): 569-76.

85. Solomon GM, Fu L, Rowe SM, Collawn JF. The therapeutic potential of CFTR modulators for COPD and other airway diseases. Current opinion in pharmacology. 2017; **34**: 132-9.

86. Loeys BL. Angiotensin receptor blockers: a panacea for Marfan syndrome and related disorders? Drug discovery today. 2015; **20**(2): 262-6.

87. Scott JP, Ji Y, Kannan M, Wylam ME. Inhaled granulocyte-macrophage colony-stimulating factor for Mycobacterium abscessus in cystic fibrosis. The European respiratory journal. 2018; **51**(4).

88. De Soyza A, McDonnell MJ, Goeminne PC, Aliberti S, Lonni S, Davison J, et al. Bronchiectasis Rheumatoid Overlap Syndrome Is an Independent Risk Factor for Mortality in Patients With Bronchiectasis: A Multicenter Cohort Study. Chest. 2017; **151**(6): 1247-54.

89. Shah PL, Mawdsley S, Nash K, Cullinan P, Cole PJ, Wilson R. Determinants of chronic infection with Staphylococcus aureus in patients with bronchiectasis. The European respiratory journal. 1999; **14**(6): 1340-4.

90. Tan WC, Hague CJ, Leipsic J, Bourbeau J, Zheng L, Li PZ, et al. Findings on Thoracic Computed Tomography Scans and Respiratory Outcomes in Persons with and without Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study. PloS one. 2016; **11**(11): e0166745.

Figure and Table Legends

Table 1. Clinical features associated with specific etiologies in bronchiectasis. Note that patients do not always present with classic features and therefore the absence of these signs cannot be used to exclude a specific etiology in bronchiectasis. Consensus guidelines recommend standardized testing irrespective of “clinical phenotype”.

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 airways phlegm disrupt normal host defenses, renderings the airways vulnerable to infection, which can become persistent. This, in turn, incites an inflammatory response causing injury and abnormal remodeling of the airways leading to bronchiectasis.

Figure 2. CFTR mutation classification. Cystic fibrosis transmembrane conductance regulators (CFTR) mutation classification based on molecular defect. These molecular defects correspond to therapeutic approaches to restore the quantity of protein and/or its function resulting in genotype specific CFTR modulator drugs used alone (ivacaftor) or in combination (lumacaftor/ivacaftor, tezacaftor/ivacaftor). Adapted from [83]

Figure 3. Ciliary dyskinesia gene classifications. Defects in cilia genes can be classified based on ultrastructural effects seen on cross sectional examination of cilia with electron microscopy. Note that some genes can be mutated without obvious structural abnormalities. Adapted from [84]

Figure 4. Potential endotypes for idiopathic bronchiectasis patients with pulmonary NTM infections. Characterization with biomarker measurements of sweat chloride, nasal NO, ciliary beat frequency, and body morphometrics coupled with the presence of relevant genetic variants may allow therapeutic targeting based on predominant endotype. Examples would be the potential use of CFTR modulators in patients that have a CF-predominant endotype [85], sildenafil or other nitric oxide pathway agonists for cilia-predominant endotype [22], TGF-beta attenuators such as losartan for heritable connective tissue-predominant endotype [86], and immune modulators such as GMCSF for immune deficient predominant endotype [87]

Table 1. Clinical features associated with specific etiologies in bronchiectasis.

Etiology	Age of onset	Radiology	Microbiology	Symptoms/features	Physiology/ lung function
Idiopathic	Postmenopausal females Any age	Any radiological pattern	*P. aeruginosa* *H. influenzae* Any pathogens or none	Any	Any
Postinfective	Any age	Any pattern Unilobar	Any pathogen or none	Should typically have onset of symptoms closely following a severe infection	Any
Connective tissue disease	Any	Any	Any	Poor prognosis/rapidly progressive Features of systematic disease[88]	Airflow obstruction (but other patterns seen)
Immunodeficiency	Primary immunodeficiency often young age	Lower lobe	Any	Frequent exacerbations Pneumonia Non-respiratory infections	Airflow obstruction

	Secondary immunodeficiency at any age				
ABPA	Any	Central bronchiectasis Infiltrates	Classically *Staphylococcus aureus*[89]	Thick sputum Wheeze Recurrent exacerbations Background asthma	Airflow obstruction
NTM	Postmenopausal females	Middle lobe and lingula bronchiectasis, tree in bud, nodular changes	In addition to NTM, may have typical bacteria such as *P. aeruginosa*	Dry bronchiectasis. Chronic cough, malaise, weight loss and systemic features Low BMI, scoliosis, pectus excavatum	Any
Primary ciliary dyskinesia	Usually presents in childhood	Middle or lower lobes	*H. influenzae* Any	Chronic rhinosinusitis, recurrent otitis media	Any

COPD	Smokers/ ex-smokers >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)[90]
Inflammatory bowel disease	Any	Any lobes affected. Bronchiolitis. May be other features of IBD 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	*P. aeruginosa* *S. aureus* Others	Rhinosinusitis Infertility Pancreatitis Malabsorption/GI symptoms	Airflow obstruction

Figure 1. Model of pathogenesis of bronchiectasis.

Alternative Figure 1

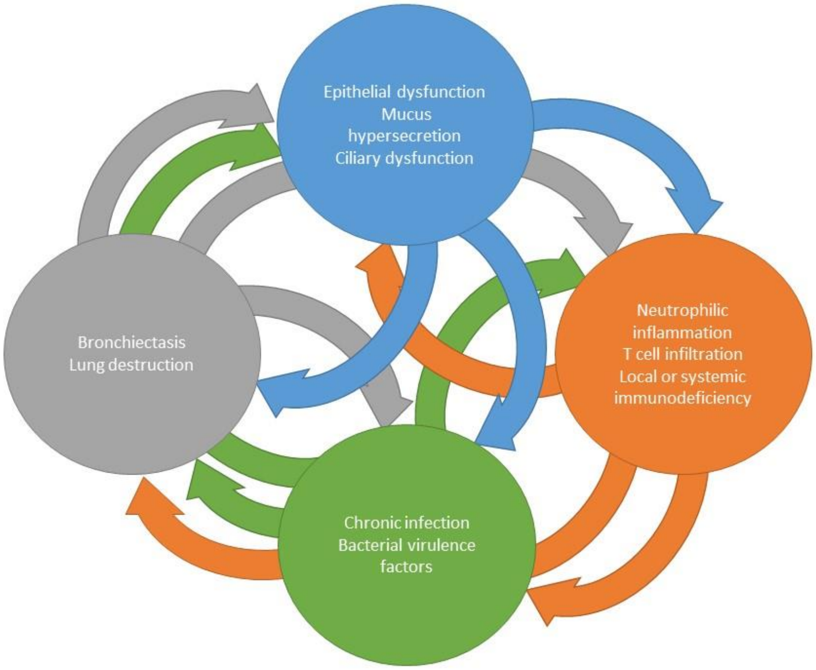
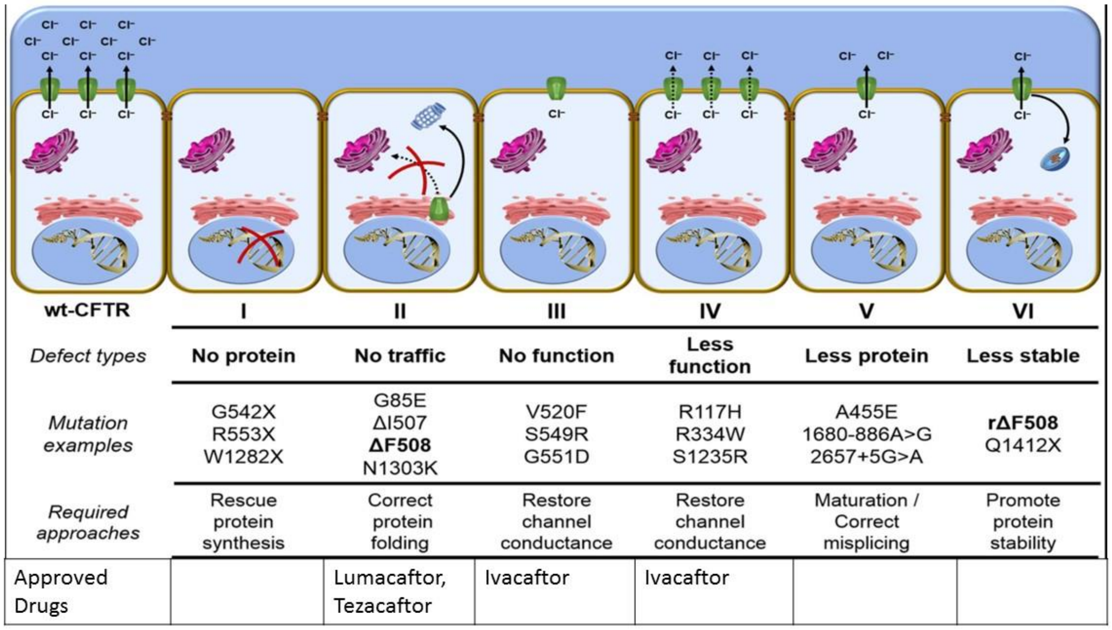


Figure 2. CFTR mutation classification



	I	II	III	IV	V	VI
wt-CFTR						
Defect types	**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples	G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches	Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability
Approved Drugs		Lumacaftor, Tezacaftor	Ivacaftor	Ivacaftor		

Figure 3. Ciliary dyskinesia gene classifications.

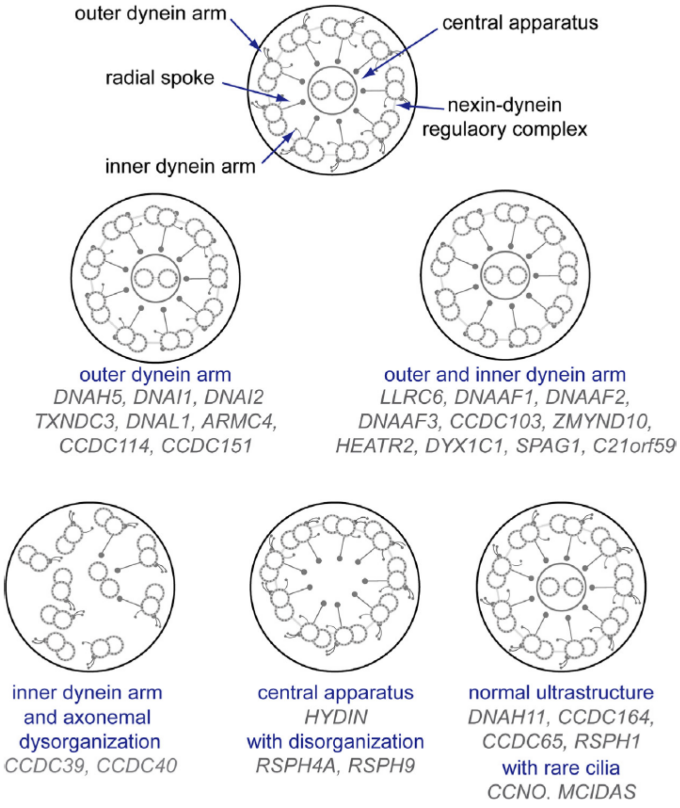


Figure 4. Potential endotypes for idiopathic bronchiectasis.