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Basic, translational and clinical aspects of bronchiectasis in adults

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Bronchiectasis is an underdiagnosed and heterogeneous disorder. Inflammation is a key driver of bronchiectasis and represents a therapeutic target for current and new treatments.
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Abstract

Bronchiectasis is a common progressive respiratory disease with recognisable radiological abnormalities and a clinical syndrome of cough, sputum production and recurrent respiratory infections. Inflammatory cell infiltration into the lung, in particular neutrophils, is central to the pathophysiology of bronchiectasis. Herein we explore the roles and relationships between infection, inflammation and mucociliary clearance dysfunction in the establishment and progression of bronchiectasis. Microbial and host-mediated damage are important processes underpinning bronchiectasis and the relative contribution of proteases, cytokines and inflammatory mediators to the propagation of inflammation is presented. We also discuss the emerging concept of inflammatory endotypes, defined by the presence of neutrophilic and eosinophilic inflammation, and explore the role of inflammation as a treatable trait. Current treatment for bronchiectasis focuses on treatment of underlying causes, enhancing mucociliary clearance, controlling infection and preventing and treating complications. Data on airway clearance approaches *via* exercise and mucoactive drugs, pharmacotherapy with macrolides to decrease exacerbations and the usefulness of inhaled antibiotics and bronchodilators are discussed, finishing with a look to the future where new therapies targeting host-mediated immune dysfunction hold promise.

Introduction

We live in a toxic environment. Our bodies, especially our lungs, are constantly exposed to a wide array of incursions from the environment. These allergens, pollutants and infectious agents, to which we respond idiosyncratically, can regulate a person's balance between immune homeostasis and dysregulation. A combination of many factors, ranging from genetics, microbiota, innate immune response activity and lifestyle, determines overall immunity, health, wellbeing and longevity or, in the case of imbalances between these factors, ill health and disease. Bronchiectasis can be considered a consequence of a dysregulated interaction between these attributes.

Bronchiectasis is a common progressive respiratory disease that is likely to be under-recognised and under-diagnosed. The disease is characterised by permanent dilatation of the bronchi and presents with a clinical syndrome of cough, sputum production and recurrent respiratory infections. The diagnosis is made by computed tomography and many patients may be initially diagnosed with other respiratory conditions, such as COPD and asthma. It was once considered an orphan disease and, although some cases remain idiopathic, much is now known about the underlying causes of bronchiectasis and, importantly, our knowledge of how to treat the disease is improving.

Chronic lung infections are polymicrobial, complex and challenging to treat. Polymicrobial infections arise from diverse sources, can be impacted by concomitant antibiotic treatment and often involve codetection of

both anaerobic and aerobic species; infection is a central tenet of bronchiectasis. The treatment and management of bronchiectasis requires a truly precision medicine approach incorporating clinical observation, clinical chemistry, immunology, microbiology, radiology, assessment of diet, exercise and lifestyle in combination with patient-reported symptoms, behaviours and quality of life issues.

Given the importance of bronchiectasis as an increasingly commonly recognised clinical entity for which there are new and emerging treatments, this article provides details on the molecular and cellular mechanisms underlying its pathophysiology and presents recent clinical data on management of patients diagnosed with the disease. Herein, having performed searches in PubMed for bronchiectasis AND/OR inflammation AND/OR infection AND/OR clinical trials, between 1991 to present, with two thirds of the citations presented published since 2016, we explore the roles of infection in bronchiectasis including an overview of microbial-derived factors. Host-mediated damage is also an important process underpinning bronchiectasis and the roles of proteases, cytokines, chemokines and other inflammatory mediators in the propagation of inflammation is presented. Both eosinophilic and neutrophilic endotypes are covered and inflammation is proposed as a therapeutic target in bronchiectasis.

Biological mechanisms underpinning bronchiectasis

There is no typical bronchiectasis patient. This is due to the fact that it is a highly heterogeneous disorder that can develop due to many different causes (reviewed in [1]). For example, bronchiectasis can occur post-infection with bacteria, viruses or mycobacteria, or it can manifest as a secondary feature of lung diseases such as COPD or asthma. Other causes include inflammatory, allergic and autoimmune processes, as well as congenital, genetic or structural abnormalities or obstructions in the respiratory tract. Cystic fibrosis (CF) is a genetic lung disease that causes bronchiectasis and, similar to some other genetic lung diseases such as primary ciliary dyskinesia, can be considered as an exemplar for many of the hallmarks of bronchiectasis. In some patients, the cause is idiopathic. Although it might appear that there is little to group these seemingly unrelated causes, in fact, all bronchiectasis sufferers share radiological abnormalities indicative of the disease and characteristics that are measurable by clinical assessment.

In addition, regardless of the disparate causes of bronchiectasis lung disease, there are four key aspects to the pathophysiology of the disease that appear to be common across all patient subgroups that are independent of cause, age, race or gender. These are infection, inflammation, mucociliary clearance dysfunction and structural lung damage (figure 1). Indeed, each one of these processes is closely interlinked with all of the others within the bronchiectasis lung and their inter-relationships underpin the phenomenon of the “vicious vortex”; a term coined to explain the complex mechanisms active and evident in the lung that promote development and persistence of bronchiectasis [2].

Infection

Infections due to bacteria, viruses, fungi or mycobacteria are associated with the establishment of bronchiectasis as well as exacerbations of the disease [3–8]. The most common bacteria identified in airway secretions from patients with established bronchiectasis are Gram-negative proteobacteria, especially *Pseudomonas aeruginosa* and *Haemophilus influenzae*, but also *Moraxella catarrhalis*, Enterobacteriacae and Gram-positive *Staphylococcus aureus* and *Streptococcus pneumoniae*. Bacterial infection of the lung signals the recruitment of inflammatory cells, especially neutrophils. Ideally, these neutrophils should fight the infection; however, in the bronchiectasis lung it appears they actually have many deleterious effects (detailed in the next section). Furthermore, the bacteria themselves can also cause direct harm within the lung.

For example, chronic *H. influenzae* and *P. aeruginosa* lung infections can directly cause tissue injury enabling them to survive in hostile microenvironments within the lung. *H. influenzae* can interfere with ciliary beat frequency *via* inhibition of protein kinase Cε and thereby contribute to the impairment of mucociliary clearance [9]. *P. aeruginosa* pyocanin has a similar effect [10]. Elastase from *P. aeruginosa* can degrade collagens III and IV and laminin in the extracellular matrix and cleave and inactivate the anti-neutrophil elastase (NE) capacity of the serine antiprotease, elafin [11–13].

Biofilms are also important. These have been found involving both *H. influenzae* and *P. aeruginosa* in patients of all ages with bronchiectasis and are now recognised as playing a critical role in establishing chronic lung infections [14, 15]. Biofilms utilise extracellular DNA (eDNA) released from neutrophils (see below) in their formation and allow bacterial communities to survive physical and chemical stresses within the lungs, while also altering their physiology and providing protection against host defences and antibiotic treatments [16].

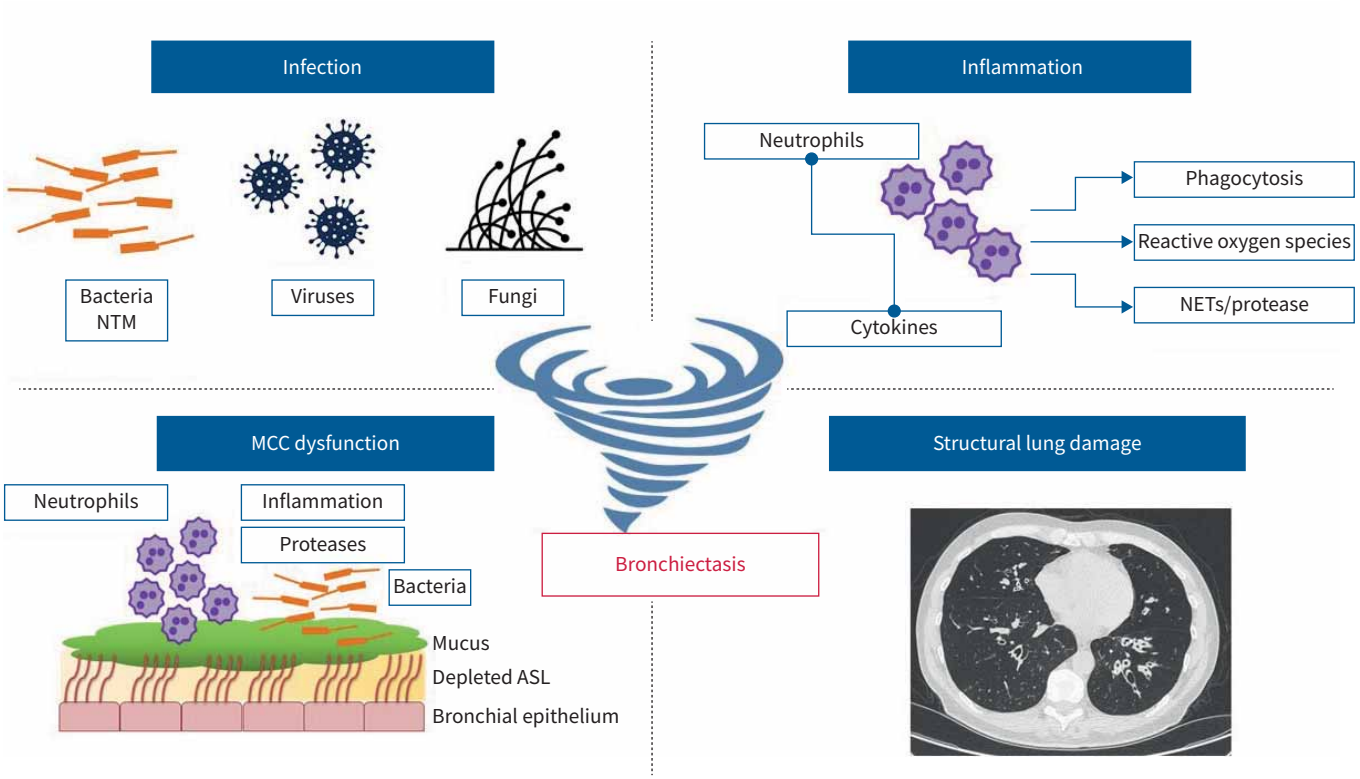

FIGURE 1 The four key aspects underpinning the vicious vortex of bronchiectasis. Pulmonary infection and inflammation, mucociliary clearance (MCC) dysfunction, and structural lung damage are common features of the pathophysiology of bronchiectasis regardless of cause. The interactions between these four aspects are not best represented as a cycle; this is due to the fact that each of the individual components can independently affect all of the other aspects and therefore it is better described as a "vicious vortex". ASL: airway surface liquid; NET: neutrophil extracellular trap; NTM: nontuberculous mycobacteria.

Overall, infection leads to the recruitment of neutrophils (*i.e.* inflammation). Certain bacteria can also cause direct structural damage to the lung and most infections can impact mucociliary clearance dysfunction. This is the essence of the vicious vortex wherein each component is related to or impacts upon another aspect of the process (figure 1).

Inflammation

Bacterial load correlates with markers of airway inflammation [17]. Neutrophils are the most abundant inflammatory cell in the bronchiectasis airway and these cells are believed to be key drivers of disease severity and progression. Nevertheless, eosinophils are also known to be important and an elevated blood eosinophil count and other markers of T-helper cell type 2 (Th2)-mediated inflammation are elevated in up to 30% of cases (discussed in more detail later). In response to various cytokines (mainly chemokine (C-X-C motif) ligand 8/interleukin (IL)-8, IL-1β, IL-17 and tumour necrosis factor-α) and chemotactic factors (*e.g.* leukotriene B4), neutrophils are recruited into the lung where they should perform a number of key functions, as follows [18, 19]: phagocytosis of bacteria; degranulation leading to the release of reactive oxygen species and proteases; and the generation of neutrophil extracellular traps (NETs). NETs are webs of DNA, histone proteins and neutrophil proteases, predominantly NE, the function of which is to trap and kill microbes [20]. The presence of NETs is associated with "severe" bronchiectasis. Each of these three pathways can be impaired in bronchiectasis, as evidenced by decreased pathogen clearance due to inadequate or faulty phagocytosis, structural damage due to abnormally high levels of neutrophil granule contents being released into the lung and impaired bacterial killing, and greater host damage as a result of aberrant NETs. Beyond this, overall neutrophil numbers are increased due to persistent neutrophil recruitment and impaired neutrophil apoptosis and clearance by macrophages [21–23]. Many of these effects are linked to an overabundance of neutrophil-derived NE, which can cleave and inactivate host proteins including cell receptors involved in efferocytosis, antimicrobial peptides and extracellular matrix proteins. Importantly, *P. aeruginosa*, *Haemophilus* and *S. aureus* in addition to other pathogens can

promote NET formation, utilise eDNA for bioflm formation, evade NET-mediated killing and/or actually degrade NETS, and thereby evade their effects [16, 24–29].

Mucociliary clearance dysfunction

Mucociliary clearance is the mechanism by which airway mucus traps debris and pathogens and removes these upwards out of the lung *via* the co-ordinated beating of cilia on epithelial cells [30]. This process is impaired in bronchiectasis. The mechanism underpinning this defect has been well studied in the CF lung, where the airway surface liquid layer is dehydrated and viscous as a result of defective CF transmembrane conductance regulator (CFTR) and overactivation of the epithelial sodium channel [31]; there is more mucus than normal due to upregulation of mucin gene expression by NE, more mucus-producing cells as a result of goblet cell hyperplasia and metaplasia, and the mucus is more viscous than normal due to the acidic pH within the CF lung [32, 33]. In bronchiectasis related to diseases other than CF, similar processes occur that may be related to primary or secondary decreased ciliary function and loss of ciliated cells in addition to inflammation-related mucus hypersecretion and dehydration including acquired CFTR dysfunction [34–37].

Structural lung damage

Structural lung damage can be both a cause and a consequence of bronchiectasis. Causes include pre-disposing genetic conditions such as CF or primary ciliary dyskinesia, congenital malformations, bronchial obstruction, connective tissue disease or post-infectious damage following, for example, pneumonia or tuberculosis. Structural lung damage as a consequence of bronchiectasis can be linked to infection, *e.g.* bacterial product effects on cytotoxicity and cilia function, inflammatory effects – in particular the higher than normal NE levels and ineffective NETs [38], and acquired mucociliary clearance dysfunction due to both infection and inflammation.

Bronchiectasis is associated with progressive loss of elastin and collagen mediated mainly by host proteases belonging to the serine, cysteine and metalloproteinase classes [39], all of which can be increased in bronchiectasis-related lung disease [38]. NE, in particular, has been well studied in this regard and increased levels of NE within the lung correlate with early bronchiectasis [40–42]. Not only can NE degrade elastin and collagen, but it also destroys the airway architecture *via* cleavage of the structural proteins laminin and fibronectin; cathepsins S and C display similar behaviour [43]. Matrix metalloproteinases (MMPs) have roles in inflammation, tissue remodelling and repair. MMP-7, for example, has a key role in post-injury re-epithelialisation and facilitates wound closure *via* syndecan-1/α2β1 integrin [44, 45]. Therefore, given the beneficial role of some host proteases in the repair of structural damage, it is the balance between protease levels and their cognate inhibitors, *i.e.* activity rather than levels, that will ultimately determine whether the overall effects are destructive or not.

Clinical challenges in bronchiectasis

Understanding the fundamental biology, microbiology and immunology of the bronchiectatic airway helps to contextualise the clinical challenges encountered in managing the disease [46]. The majority of patients with bronchiectasis have chronic productive cough, with sputum viscosity, purulence and volume contributing to poor quality of life on a daily basis and worsening during exacerbation [47–49].

Exacerbations are a key driver of disease progression, with patients who experience frequent exacerbations being at higher risk of future hospitalisation, poorer quality of life and even mortality [50]. Management of the condition is challenging because of the need to resolve the great heterogeneity of the disease. Two patients with similar symptoms may have entirely different underlying conditions, comorbidities, lung function, radiology, microbiology, disease severity, underlying lung inflammation, expectations and treatment adherence as well as social circumstances [51]. The heterogeneous nature of the disease is therefore considered the major clinical challenge [2, 52]. Multidimensional severity scores such as the bronchiectasis severity index allow stratification for future risk but have not been shown to identify patients who are likely to respond to specific treatments [53]. Better tools to stratify the disease are required, which may include clinical tools, biomarkers and imaging modalities.

Current therapies

Current treatment for bronchiectasis focuses on treatment of underlying causes, enhancing mucociliary clearance, controlling infection and preventing and treating complications [46]. The goals of treatment are to preserve lung function, halt disease progression, improve quality of life as well as preventing hospitalisation and premature mortality. Initial assessment of patients should include assessment of severity of the disease, using multidimensional scales or their individual components such as quantifying the number of exacerbations, hospitalisations, functional limitation and radiological severity among other

parameters [53]. Lung function, sputum culture and standardised testing for underlying causes are also essential in the initial assessment of patients [46]. Treatment of the underlying cause where possible is fundamental and means that patients must be systemically tested for immunodeficiency and allergic bronchopulmonary aspergillosis in all cases since these cannot be reliably identified by clinical features [46, 54]. Testing for other underlying conditions is targeted based on clinical features and risk factors. Most underlying causes are underdiagnosed due to a lack of systematic testing [55, 56]. Underdiagnosis of primary ciliary dyskinesia was recently documented in the UK despite well-developed diagnostic services [55].

Airway clearance is the mainstay of treatment and is individualised to the patient according to their symptoms and severity of mucus obstruction [57]. Trials of airway clearance in bronchiectasis are small but show convincing benefits, such as the recent trial by Munoz *et al*. [58], where 22 patients were randomised to airway clearance (l'expiration lente totale glotte ouverte en décubitus latéral – ELTGOL exercises) or "placebo exercises" for 12 months, demonstrating clear reductions in exacerbations and improved symptoms. Mucoactive drugs such as hypertonic saline or carbocisteine/*N*-acetylcysteine may be used to alter mucus properties and enhance clearance [46]. Inhaled mannitol failed to show a reduction in the frequency of exacerbations in the largest trial of mucoactive drugs in bronchiectasis to date [59], but a *post hoc* analysis suggests that patients with the most severe symptoms do benefit [60]. It makes logical sense that mucoactive therapies would be most effective in patients who have severe mucus symptoms despite airway clearance. Large trials of hypertonic saline and carbocisteine are ongoing at the time of writing.

Macrolides are the most effective pharmacotherapy for bronchiectasis based on the results of randomised trials [61]. They reduce exacerbations by approximately 50% (adjusted 0.49, 95% CI 0.36–0.66; p<0.0001 from three trials with 341 participants) in an individual participant data meta-analysis of trials of at least 6 months duration [61]. Treatment also improves symptoms. It is intriguing that macrolides appear to be effective in all patient subgroups, including those with macrolide "resistant pathogens" such as *P. aeruginosa* [61]. The fact that efficacy increases with increasing levels of C-reactive protein in blood and treatment works in the absence of conventional bacterial infection, as well as the well-reported immunomodulatory effects of macrolide, raise the high likelihood that macrolide benefits are not directly related to antimicrobial effects. The potential nonantibiotic effects of macrolides are reviewed extensively in [62]. While macrolides have been shown to be highly effective, unanswered questions regarding macrolides include the optimal point in the disease course in which to introduce them, whether treatment needs to be long term or can be discontinued and whether there is loss of efficacy or clinically relevant bacterial resistance over time.

Inhaled antibiotics are recommended in clinical guidelines for patients with *P. aeruginosa* infection and at least three exacerbations per year in patients already practicing regular airway clearance based on observations that they reduce bacterial load and may reduce exacerbations [46, 63, 64]. A meta-analysis of 16 trials including 2597 patients concluded that inhaled antibiotics (including aminoglycosides, aztreonam, fluoroquinolones and polymyxins) all consistently reduced bacterial load in sputum, but with highly inconsistent results in terms of reduction in exacerbations or improvements in symptoms [65]. The overall pooled results of the meta-analysis suggest a decreased risk of exacerbations (risk ratio 0.85, 95% CI 0.74–0.97; p=0.015) with a great effect on severe exacerbations. Inhaled antibiotics are rarely reported to significantly reduce symptoms in clinical trials, which is in contrast to clinical experience that patients often respond [66]. Crichton *et al*. [67], investigated this and in a *post hoc* analysis of trials of inhaled aztreonam showed that inhaled antibiotics improve cough, sputum volume and sputum colour, but do not improve breathlessness, chest discomfort or wheeze, leading to limited changes on aggregate symptom score. It is clear that not all patients with airway infection respond positively to inhaled antibiotics, indicating that pathogens drive symptoms and exacerbation risk in some patients but not all. Higher bacterial load at baseline may predict the response to inhaled antibiotics but is not a widely used clinically biomarker [68]. The study by Keir *et al*. [69], which examined sputum proteomics following antibiotic therapy, identified that patients with *P. aeruginosa* had a lesser response to antibiotics in terms of reduced proinflammatory and increased anti-inflammatory proteins [24].

Inhaled corticosteroids (ICS) are not recommended for bronchiectasis except in patients with underlying asthma or COPD according to international guidelines [46]. ICS have important effects on eosinophils, inducing apoptosis and depletion of these cells [70]. Reduced proinflammatory cytokines from T-cells, epithelial cells and macrophages, depletion of mast cells and dendritic cells, plus reduced mucus secretion are potentially beneficial effects of ICS in the airway. Clinical evidence that corticosteroids improve outcomes in bronchiectasis are lacking. In COPD, a disease with an overlapping airway inflammatory profile with bronchiectasis, only patients with raised blood eosinophil counts, and therefore a high

likelihood of airway eosinophilia, derive a benefit from ICS in terms of reduced exacerbations [71]. Overuse of ICS in bronchiectasis should be avoided in view of the known association between ICS use and pneumonia and mycobacterial infection among other adverse effects [72–74]. Bronchodilators should theoretically improve breathlessness and, *in vitro*, long-acting muscarinic antagonists reduce mucus production [75]. In the largest study of bronchodilators to date, tiotropium improved lung function but did not reduce exacerbations or improve symptoms in 90 patients with bronchiectasis [75, 76]. The approach to the investigation and management of bronchiectasis is summarised in figure 2.

Endotyping bronchiectasis and precision medicine

The only way to effectively manage a disease as heterogeneous as bronchiectasis is to practice precision medicine [77]. Endotyping (defined as classifying disease through underlying biological mechanisms), phenotyping (defined as classifying disease through observable patient characteristics) and identifying treatable traits (defined as therapeutic targets identified through either a phenotype or an endotype and using a validated biomarker) are methods used to guide precision medicine strategies [78, 79].

Conventionally, the disease is classified by the underlying disease, *e.g.* idiopathic, post-infective, autoimmune and/or immunodeficiency associated bronchiectasis. This is important and some of these underlying causes impact the treatment of the bronchiectasis but the majority do not. There is a high degree of heterogeneity, even within patients who have the same aetiology. Patients can also be classified by their microbiology, with *P. aeruginosa*-infected patients having a worse prognosis [80]. Nontuberculous mycobacterial infection likewise has a distinct clinical course, morphometric associations and genetic background [81, 82]. Sequencing of the lung microbiome indicates that proteobacteria-dominant patients with *Pseudomonas* in particular have more severe disease and are clearly different to patients with *Firmicutes*-dominant disease (the most common clinically relevant organisms in bronchiectasis patients within this genus are streptococci and staphylococci), although the loss of commensal anti-inflammatory bacteria may also be important [83–85]. Finally, there are clinical phenotypes that can be seen as treatable traits, such as frequent exacerbators, patients with dominant upper airway disease and the overlap between bronchiectasis and COPD [2, 77, 86]. A comprehensive listing of possible treatable traits is given in table 1. The concept encourages a holistic approach to patient care centred around the patients' major clinical problems, such as frequent exacerbations or symptoms, and the treatable components of the disease,

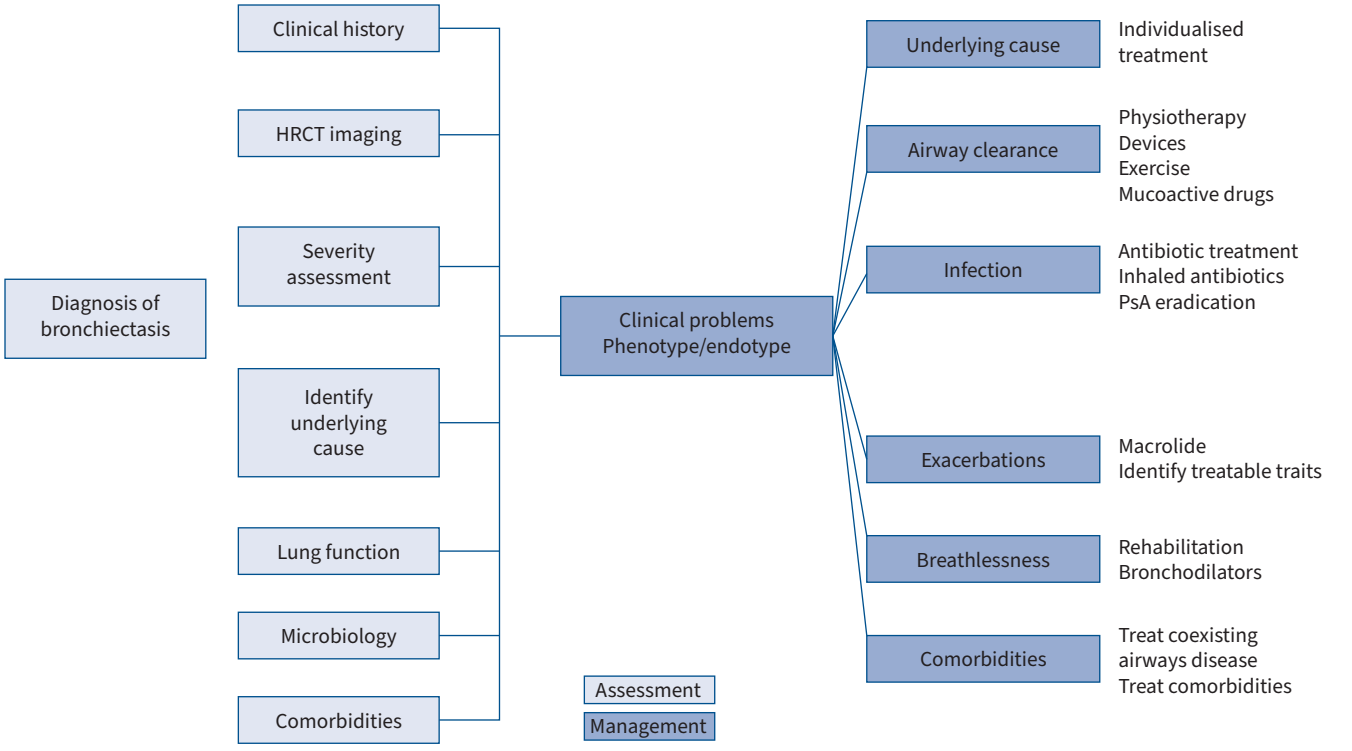

FIGURE 2 Diagnosis and management of bronchiectasis. Schematic summarising the key aspects in the assessment and treatment of bronchiectasis. HRCT: high-resolution computed tomography; PsA: *Pseudomonas aeruginosa*.

TABLE 1 Treatable traits in bronchiectasis divided into pulmonary, aetiology related, extrapulmonary and behavioural/lifestyle as originally proposed by Agusti *et al.* [87].

Treatable trait	Identification	Treatment	Potential benefit
Pulmonary traits			
Infection	• Regular sputum culture • Sputum culture • Bacterial exacerbations	• Airway clearance • Antibiotic treatment for exacerbation • Long-term antibiotics	• Reduced exacerbations and reduced cough and mucus symptoms
Pseudomonas aeruginosa infection	• Regular sputum culture	• Airway clearance • Eradication at first isolation • Long-term antibiotics	• Reduced exacerbations and reduced cough and mucus symptoms • Improved quality of life
Mucus hypersecretion	• Volume and colour of sputum • Quality of life • CT scan showing mucus plugging	• Airway clearance • Devices • Mucoactive drugs • Anti-inflammatories (including macrolides)	• Reduce sputum volume • Improve airway clearance/ expectoration • Improve quality of life
Airflow obstruction	• Lung function testing	• Exercise/rehabilitation • Bronchodilators • Smoking cessation	• Improve symptoms and quality of life
Neutrophilic inflammation	• Sputum colour and volume • Frequency of exacerbations	• Macrolides • Antibiotic treatment for exacerbations/infection	• Prevent exacerbations and improve quality of life
Eosinophilic inflammation	• Blood eosinophil count >300 cells·μL^{-1} and frequent exacerbations	• Inhaled corticosteroids • Anti-IL5/anti-IL5 receptor monoclonal antibodies	• Prevent exacerbations and improve symptoms
Cough hypersensitivity	• Clinical features • Cough challenge	• Airway clearance • Physiotherapy	• Reduce exacerbations • Improve quality of life
Asthma	• Variable airflow obstruction • Bronchodilator reversibility	• Inhaled corticosteroids • Leukotriene receptor antagonists • Monoclonal antibodies	• Improve quality of life
NTM infection	• Positive cultures • Clinical and radiological features consistent with NTM pulmonary disease	• Antibiotic treatment • Airway clearance	• Improve quality of life • Achieve microbiological remission
Aspergillus sensitisation	• Elevated IgE and specific IgE to *Aspergillus* • Symptoms and exacerbations	• Oral corticosteroids • Antifungals • Inhaled corticosteroids	• Reduce exacerbations • Improve symptoms and quality of life
Bronchial hyperreactivity	• Bronchial challenge test	• Inhaled corticosteroid	• Reduce exacerbations
Respiratory failure	• Arterial oxygen and carbon dioxide	• Long-term oxygen or noninvasive ventilation	• Improve quality of life and/ or potentially survival
Aetiology related			
Immunodeficiency	• Serum immunoglobulins and functional antibodies	• Refer to immunology • Immunoglobulin replacement	• Reduce exacerbations and disease progression
Cystic fibrosis	• Clinical features • CFTR genetics and sweat chloride concentration	• Refer to CF clinic • CFTR modulators • DNase	• Improve lung function, quality of life and survival
Primary ciliary dyskinesia	• Clinical features • Nasal NO • Multidisciplinary diagnostics including high-speed video microscopy, EM, immunofluorescence and genetics	• Genetic counselling • Intensified airway clearance • Management of upper airway symptoms • Early introduction of prophylactic antibiotics	• Improve quality of life • Reduce disease progression • Prevent exacerbations
Inflammatory bowel disease	• Clinical features including classically sterile bronchorrhoea	• Refer to gastroenterology • Immunosuppression • Respiratory symptoms treated with inhaled corticosteroid	• Improve quality of life and symptoms
Connective tissue disease	• Clinical features and autoantibodies	• Refer to rheumatologist • Immunosuppressive drugs with early introduction of prophylactic antibiotic	• Improve quality of life • Prevent exacerbations

Continued

TABLE 1 Continued

Treatable trait	Identification	Treatment	Potential benefit
Extrapulmonary traits			
Depression/anxiety	• Symptoms/patient history • Questionnaires	• Cognitive behaviour therapy • Counselling • Pharmacotherapy • Support groups	• Improve quality of life
Obesity/low BMI	• BMI	• Nutritional evaluation • Good diet • Regular physical activity	• Improve quality of life
GORD	• Clinical features • Endoscopy • pH monitoring	• Lifestyle advice • Proton pump inhibitor or equivalent • Surgery	• Improve quality of life • Reduce exacerbations
Cardiovascular disease	• Clinical features • Echocardiography and ECG • BNP • Stress testing	• Pharmacotherapy for heart failure of ischaemic heart disease • Refer to cardiology	• Improve exercise capacity and quality of life
Rhinosinusitis	• Clinical features • Imaging	• Nasal steroids • Leukotriene receptor antagonists • Antihistamines • Macrolides • Surgery	• Improve quality of life • Reduce exacerbations
Anaemia	• Full blood count • Reticulocyte count • Haematinics	• Treat underlying cause	• Improve exercise capacity
Behaviour/lifestyle traits			
Exercise deconditioning	• Cardiopulmonary exercise testing • Other exercise tests	• Regular exercise • Pulmonary rehabilitation	• Improve exercise capacity and quality of life
Treatment adherence	• History • Electronic prescribing data	• Education • Self-management • Shared decision making	• Improve quality of life • Prevent exacerbations
Air pollution exposure	• Exposure to pollutants	• Reduce exposure	• Reduce exacerbations
Smoking (including vaping and electronic cigarettes)	• Patient reported	• Smoking cessation including replacements and pharmacotherapy	• Improve quality of life and lung function • Reduce exacerbations

Table adapted from Boaventura *et al.* [88]. BMI: body mass index; BNP: brain natriuretic peptide; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CT: computed tomography; DNase: deoxyribonuclease; EM: electron microscopy; GORD: gastro-oesophageal reflux disease; IL: interleukin; NO: nitric oxide; NTM: nontuberculous mycobacteria.

which may be addressed. It reminds the clinician of the need to individualise care; for example, the European Respiratory Society guidelines for bronchiectasis would suggest the addition of a macrolide or an inhaled antibiotic for patients with three or more exacerbations per year despite regular airway clearance. The treatable traits approach would encourage clinicians to consider, as well as antibiotic treatment, adherence, treating comorbidities such as rhinosinusitis and alternative therapies for specific endotypes (such as ICS in inflammatory bowel disease associated bronchiectasis, asthma or blood eosinophilia). The choice of treatment will take into account patients' severity of disease and a hierarchy of interventions with the simplest interventions with the greatest benefit and lowest burden and risk introduced first, and high-burden interventions with more adverse effects added later. As with most aspects of bronchiectasis care, it must be acknowledged that many interventions listed in table 1 have a limited evidence base. Nevertheless, it has been shown in diseases like asthma that a treatable traits approach consisting of multiple interventions can produce clinical benefits in terms of improved asthma control even where individual components had only a small effect [89].

Inflammation may be the most powerful tool currently available to subtype the disease because of its strong links in terms of both clinical phenotype and outcomes, as well as the central nature of inflammation in the pathophysiology [24].

Neutrophilic inflammation is the dominant inflammatory endotype of bronchiectasis [90] and can be detected in clinical practice through the purulence of sputum, with the green colour of sputum deriving

from the presence of myeloperoxidase released from the primary granules of neutrophils [91]. The presence of pathogenic bacteria also indicates the likely presence of neutrophilic inflammation with neutrophil numbers and markers of activation such as NE correlating with bacterial load by culture and microbial diversity and dominance of pathogenic proteobacteria in microbiome sequencing [68, 84].

Eosinophilic inflammation can also clearly cause and exacerbate bronchiectasis, as illustrated by allergic bronchopulmonary aspergillosis, a disease driven by Th2 inflammation. Studies have shown an association between eosinophilic inflammation and mucus plugging along with the development of bronchiectasis in people with asthma [92]. Recently, work from the European Bronchiectasis Registry study group has identified an eosinophilic endotype in bronchiectasis even when asthma is excluded [93]. A study of over 1000 patients from several European countries found that sputum and peripheral blood eosinophils were correlated and that using blood eosinophil counts as a surrogate, approximately 20% of patients with bronchiectasis were eosinophilic (defined as eosinophil counts >300 cells·μl^{-1}) [93]. Interestingly, there was an association with *P.* aeruginosa infection, which has been shown to induce a Th2 response in CF as well [94]. A limitation of this multicentre study was a lack of fractional exhaled nitric oxide (F_{ENO}) measurement [93]. Oriano *et al.* [95] recently found that defining Th2-high bronchiectasis as either a raised F_{ENO} or raised eosinophil count increased the proportion of Th2-high bronchiectasis to 30%.

These data suggest that the majority of patients with bronchiectasis have neutrophilic disease, while up to 30% have Th2-high disease, which may coexist with neutrophilic inflammation or in some cases may be the dominant trait. The implications of this are that patients with dominant neutrophilic disease may respond to airway clearance, macrolides and in some cases where bacteria are the primary driver, to inhaled or long-term oral antibiotics. Where eosinophilic inflammation is present, studies suggest that ICS may improve quality of life, as recently demonstrated in a *post hoc* analysis of a trial of fluticasone in bronchiectasis patients [96], or even anti-IL5 and anti-IL5 receptor monoclonal antibody therapy, which has been used off-label in a number of cohorts with reportedly high efficacy [97].

Perspective and future therapies

There remain no licensed therapies for bronchiectasis and there is a need for the development of novel therapies. A phase 2 trial of dipeptidyl peptidase-1 inhibitor, brensocatib, provides an insight into the role of neutrophil serine proteases in bronchiectasis. The WILLOW phase 2 trial enrolled 256 patients and randomised patients to either 10 or 25 mg of brensocatib or placebo [98]. Both doses prolonged the time to first exacerbation (primary outcome) compared to placebo and reductions in NE in sputum were also observed. Subsequent analysis found a remarkable relationship between NE levels and exacerbation risk [99]. In a *post hoc* analysis, it was found that patients who achieved at least one post-baseline sputum sample negative for NE (below the limit of quantification of the assay) rarely experienced exacerbations, whereas patients who remained positive for NE throughout the study had a shorter time to next exacerbation and more exacerbations over 6 months [99]. These data confirm the previous observational studies showing a direct relationship between neutrophil serine protease activity and exacerbations [100–102]. No effect of brensocatib on the respiratory symptom domain of the quality of life bronchiectasis questionnaire was observed in the WILLOW trial. Whether this reflects a true absence of an effect or a lack of statistical power in a small phase 2 study remains to be established.

Other mechanisms currently being explored in phase 1 or 2 trials include novel dipeptidyl peptidase 1/cathepsin-C inhibitors and CFTR modulation, since acquired CFTR dysfunction due to the effects of neutrophilic inflammation as well as inherited defects that do not meet the diagnostic criteria for CF are relatively common in bronchiectasis [103]. It is possible that experimental therapies based on inhalable microRNA modulators, originally developed for CFTR dysfunction in CF, could have relevance for bronchiectasis [104]. Alternatively, inhaled therapies directed at the overabundance of NE may also be worth exploring in further detail, *e.g.* alpha-1 antitrypsin augmentation therapy [105]. Alternatives to antibiotics include inhaled immunoglobulin. Anti-IL-5 receptor monoclonal antibodies are also being trialled in patients with eosinophilic bronchiectasis. The bronchiectasis pipeline is, however, relatively lacking in novel targets and there is a need for both the identification of new targets and for more early phase trials. Ongoing advocacy [106], engagement with pharmaceutical companies and efforts to streamline trial conduct are needed to encourage the development of novel therapies specifically for bronchiectasis.

Summary

Bronchiectasis is a complex disease with multiple underlying causes, diverse pathophysiological processes and limited evidence-based treatments. Progress in bronchiectasis will require integration of basic mechanistic investigations, translational and clinical science.

Points for clinical practice and questions for future research

- Bronchiectasis is an increasingly common, yet underdiagnosed and highly heterogeneous disease.
- Inflammation is a key driver of bronchiectasis; it represents a therapeutic target underpinning the effectiveness of current and developing therapies. New treatments directed at neutrophilic and eosinophilic endotypes are likely to be necessary and research to better target therapies to the right patient populations is needed.
- Precision medicine approaches will become key to improving symptomology and quality of life. The challenge for physicians is to identify the correct combination of airway clearance, mucolytic, antibiotic, anti-inflammatory and bronchodilator approaches. Corticosteroids are currently not recommended by guidelines.

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