Future Directions in Bronchiectasis Research

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KEYWORDS

• Biomarkers • Endotypes • Omics • Personalized medicine

KEY POINTS

- One of the main research priorities in bronchiectasis is to address the complexity and heterogeneity of this disease.
- In the era of multi-omics approaches, there is an urgent need to generate data to better stratify patients in endotypes.
- Personalized medicine is required, and it will be achieved by the application of omics technologies and stratification tools to uncover such biomarkers.
- Future research studies involving cluster strategies and network analyses are needed to integrate data for improving our knowledge about the biology of bronchiectasis.

INTRODUCTION

Bronchiectasis is a chronic and heterogeneous inflammatory condition, characterized by the pathologic dilation of the airways, resulting in impaired mucociliary clearance and causing a cycle of recurrent exacerbations, inflammation, and destruction of the bronchial tree.[1] Until 1 decade ago, bronchiectasis was an orphan disease, but with diagnostic improvements, today it is considered a highly prevalent chronic respiratory disease that affects patient's quality of life and is associated with substantial health care costs.[2] It is caused by various etiologies, which complicates inferences from clinical trials enrolling heterogeneous populations. Importantly, to date, there are still no therapeutic options approved by American or European regulatory agencies to hinder the progression of the disease.

Nowadays, one of the research priorities in bronchiectasis is the finding of new biomarkers of disease activity.[3,4] Among the new tools used, omics technologies offer the potential for integrating a huge amount of data into systems biology, significantly improving our knowledge about the biological mechanisms in bronchiectasis. Biomarkers study using novel techniques, such as cluster strategies and network analyses,[5–7] allow the classification of patients in the so-called endotypes, defined as groups of patients based on shared biological mechanisms.[8] Identification of endotypes would improve the enrolling of patients into the right clinical trials to find new treatments and to move toward personalized medicine (**Fig. 1**). The present chapter provides a comprehensive account of the disease heterogeneity reviewing both local and systemic validated biomarkers, omics technologies, endotypes, and new treatments toward personalized medicine in the field of bronchiectasis.

VALIDATED BIOMARKERS

For years, sputum color has been the most affordable qualitative lung infection biomarker in clinical practice for patients with bronchiectasis.[9] The green color of sputum reflects pulmonary neutrophilic inflammation, through the green neutrophil protein myeloperoxidase, which is increased during exacerbations.[10] However, nowadays multiple studies have been published to find quantifiable biomarkers in blood and lung samples with a

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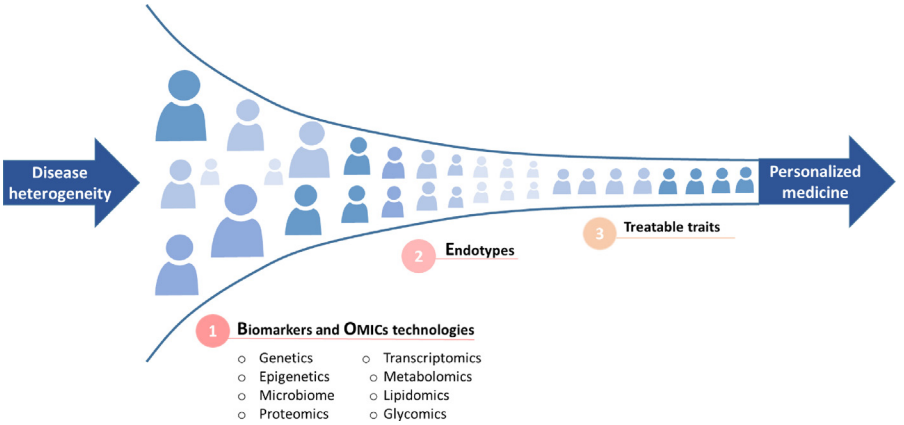

Fig. 1. Future directions of bronchiectasis research toward a personalized medicine through the application of omics technologies, the validation of new biomarkers, the identification of endotypes, and the development of new treatments. (*From* Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep 9;50(3):1700629; DOI: 10.1183/13993003.00629-2017. Reproduced with permission of the © ERS 2021 Published 9 September 2017.)

diagnostic, therapeutic, or even prognostic role of the disease, including response to treatments. These biomarkers have been associated with the different events described in the so-called Cole's vicious circle.[11] Briefly, this theory suggests that the alteration of mucociliary clearance leads to an increase in bronchial secretions, which in turn decreases the immune barrier capacity of the epithelium, thus facilitating the development of a chronic infection. This inability to eliminate pathogenic microorganisms produces a sustained inflammatory response, mainly neutrophilic,[12,13] which results in lesions of the bronchial epithelium and induces pathologic remodeling. However, a novel modification of this theory is included in the vicious vortex hypothesis, which describes that all the pathogenic components are connected to each other, making it necessary to treat various aspects of the disease and not just the infectious event.[4]

Therefore, validated biomarkers are key in the identification of endotypes. Some of the most relevant and promising biomarkers that have been proposed in stable bronchiectasis and their major associations with clinical variable are detailed in Fig. 2. This summary highlights the urgent need to expand the research into biomarkers associated with clinical outcomes and to also include the evaluation of treatment response in the studies performed.

Pulmonary Proteases

The activation of neutrophils in the lung produces the secretion of proteases such as neutrophil elastase (NE), cathepsin G, proteinase-3, and matrix metalloproteases (MMP), all of them related to the progressive epithelial damage and the increased secretion of mucus.[14] Among them, NE and MMPs have shown strong associations with clinical outcomes. NE is a protease with proinflammatory activity, which decreases the frequency of ciliary movement of epithelial cells and stimulates mucus secretion.[15,16] Under normal conditions, the action of NE is inhibited by endogenous antiproteases, such as α1-antitrypsin and the secretory leukocyte protease inhibitor (SLPI), to maintain homeostasis between protease and antiprotease activity. However, in the context of chronic inflammation, the increase in protease activity produced by the migration and persistent activation of neutrophils in the lung induces the degradation of protease inhibitors.

The imbalance that occurs between the amount of proteases and their inhibitors contributes to tissue damage, slowing the mobility of the cilia and the clearance of mucus.[16] Consequently, an increase in pulmonary concentrations of NE in patients with bronchiectasis is related to a high frequency of exacerbations, a decline in FEV_1, chronic infection by *Pseudomonas aeruginosa*, and high risk of mortality.[17–19] Furthermore, NE is one of the proteins responsible for initiating the NETosis mechanism, by which the neutrophil releases networks (NETs) composed of DNA, histones, and antimicrobial peptides (AMPs). The function of NETs is mainly to trap and eliminate

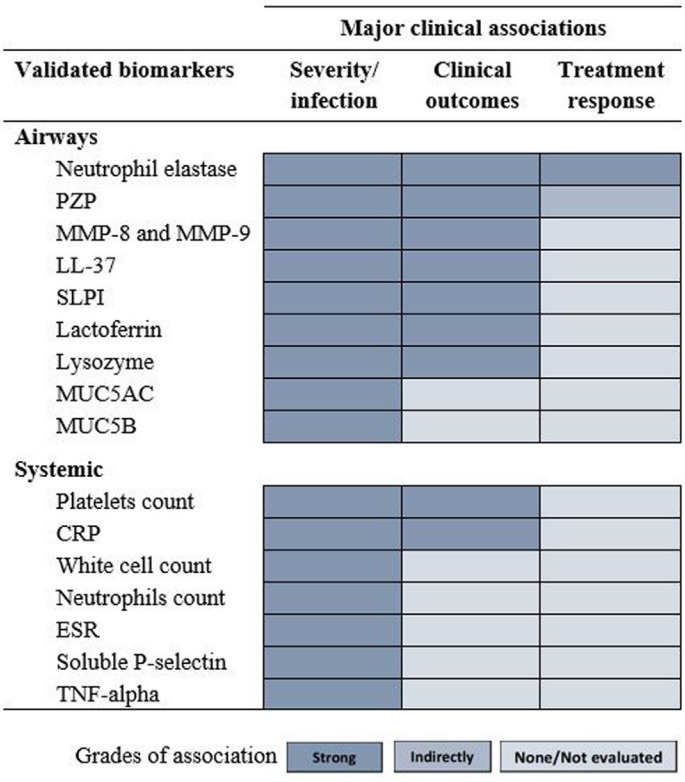

Fig. 2. Relevant protein biomarkers validated in bronchiectasis at the stable status and their associations with the major clinical variables. (*From* Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep 9;50(3):1700629; DOI: 10.1183/13993003.00629-2017. Reproduced with permission of the © ERS 2021 Published 9 September 2017.)

pathogenic microorganisms, but an excess in their production causes tissue damage and inflammation. In bronchiectasis, a massive release of NETs has been associated with the production of inflammatory mediators, the clinical severity of the patient, and the response to treatment.[20,21] Therefore, endotypes based on NE are promising as it is considered as a potential target to be inhibited.

MMP are the proteases responsible for degrading the extracellular matrix to maintain proper epithelial remodeling. To date, 28 different MMPs have been described depending on their target and their tissue origin.[22] The pulmonary production of MMPs is also highly regulated by their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]) to avoid collateral tissue damage.[23] Both MMPs and TIMPs are produced by various cell types such as neutrophils, epithelial cells, macrophages, and fibroblasts.[24]

Under normal conditions, pulmonary levels of MMPs are low and only increase during an inflammatory event. Several studies have reported elevated levels of MMP-8 and MMP-9, produced by neutrophils, in the airways of patients with bronchiectasis. Their increase has been associated with the inflammatory process and the epithelial destruction characteristic of these diseases.[25–27] With regard to the symptoms, elevated levels of MMP-8 and MMP-9 have been associated with a greater radiological extension and a greater bacterial load in sputum, worse FEV_1, greater severity of the disease, increased sputum purulence, presence of airway *P. aeruginosa* infection and prediction of future exacerbations.[28] As they are highly associated with NE, it is likely that the inhibition

of NE in these endotypes also improves the tissue damage caused by MMPs.

Mucins

Airway mucus is one of the main barriers of the immune system, and its composition mainly includes water, salt, and protein. In respiratory diseases, this mucus acquires high viscosity due to changes in its components. Mucins are glycoproteins that form the main macromolecular component of mucus and there are more than 20 genes reported encoding for these proteins. In the airways, MUC5AC and MUC5B are the mainly secreted mucins.[29,30]

Several studies have shown that the mucin concentration is significantly higher in patients with bronchiectasis than in healthy subjects and has been related to high osmotic pressure, greater viscosity and elasticity, greater inflammation, and airway infection.[30,31] Even so, the results among the different studies can lead to some controversy depending on the method of detection and quantification of pulmonary mucin concentrations.[32] This is due to the great complexity of mucins caused by their high glycosylation. However, although these techniques are complex and more studies are needed to demonstrate the role of mucins as a biomarker of clinical prognosis, they could become a potential therapeutic target in the management of secretions in these patients.

Antimicrobial Proteins and Peptides

Antimicrobial proteins and peptides (AMPs) are a diverse group of molecules that are part of the fluid that covers the epithelium and participate in innate immunity against infections.[33] They are produced during the activation of neutrophils, macrophages, and bronchial epithelial cells against pathogenic microorganisms, and are also regulated by epithelial damage, cytokines, growth factors, and nutrients such as vitamin D.[34] They not only have bactericidal activity but also proinflammatory functions. Examples of AMPs with predominantly proinflammatory function include lysozyme, lactoferrin, and cathelicidin LL-37, and those with anti-inflammatory functions include SLPI.[35,36]

In bronchiectasis, high levels of LL-37 and low levels of SLPI in sputum have been independently associated with disease severity, *P. aeruginosa* infection, and risk of exacerbation during 1 year of follow-up.[37] However, it is plausible that not only the production of AMPs is altered but also their activity is inhibited, thus favoring the development of respiratory infection. The use of cluster analysis also allowed the identification of three clusters (endotypes) based on different sputum levels of AMPs.[38] These endotypes also showed distinct profiles of inflammation, epithelial damage, and tissue remodeling markers (**Fig. 3**). Furthermore, these endotypes had different disease severity, bronchial infection, and risk to suffer from exacerbation during 1-year of follow-up.[38] Therefore, cluster analyses provide a more comprehensive understanding of the whole spectrum of host response rather than single biomarker analyses. Future research should be focused on AMPs cluster strategies based on immunologic predictors of disease severity.

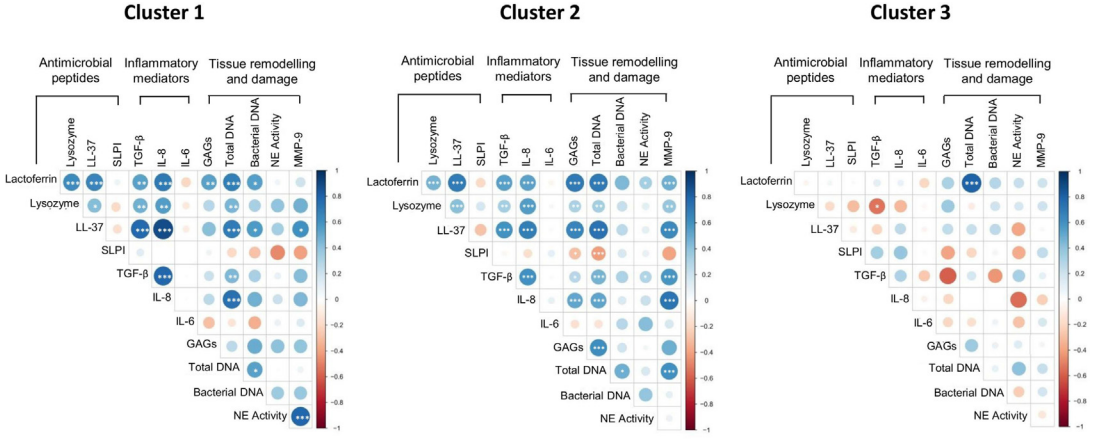

Fig. 3. Endotype research in bronchiectasis showing the presence of distinct clusters of patients based on their levels of AMPs and the differential relationships between AMPs, inflammatory mediators, and markers of tissue remodeling and damage. (*From* Perea L, Cantó E, Suarez-Cuartin G, Aliberti S, Chalmers JD, Sibila O, Vidal S. A Cluster Analysis of Bronchiectasis Patients Based on the Airway Immune Profile. Chest. 2021 May;159(5):1758-1767.)

Systemic Inflammation

The inflammatory response present in these patients has a clear predominance at the pulmonary level. However, different studies have found significantly elevated levels of systemic inflammatory markers during clinical stability and exacerbations. White blood cell count, neutrophil count, erythrocyte sedimentation rate, C- reactive protein, and several inflammatory markers such as soluble P-selectin and TNF-α concentrations in serum, have been correlated with disease severity in a stable state.[39–42] In addition, thrombocytosis during clinical stability is associated with an increased risk of severe exacerbations and mortality.[43] For this reason, platelet count could be a powerful systemic biomarker easily affordable in clinical practice. However, heterogeneity also exists in systemic inflammatory markers.[44]

In view of these findings, future directions in bronchiectasis research should include cluster strategies and network analyses based on both local and systemic biomarkers to increase our knowledge about endotype patients. Furthermore, further research involving longitudinal analysis is needed to study the stability of these clusters over time.

GENETICS AND EPIGENETICS

Recent advances in lung biology involving genetic studies have allowed to identify genetic variants associated with lung functions and to provide novel evidence for understanding the pathogenesis in airway diseases.

In 1989, genetics approaches allowed to know the mutations in the gene responsible for cystic fibrosis (CF), the most common and lethal autosomal recessive disorder in Caucasians.[45] This gene encodes for a protein called cystic fibrosis transmembrane conductance regulator (CFTR), and its mutation influences the composition and the quantity of the epithelial lining fluid.[45] Genetics studies have made it possible to consider CFTR as a therapeutic target and to develop strategies, including gene and molecular therapy, to correct this defect. Recent advances in molecular therapy, which aims to restore the CFTR function, reveal this strategy as the most successful one, with several drugs in development and already multiple commercialized highly effective corrector therapies.[46]

But not only CF takes advantage of genetic studies. Other etiologies of bronchiectasis also have a well-known associated genetic variant, such as primary ciliary dyskinesia (PCD), primary immunodeficiencies, autoimmune diseases, allergic bronchopulmonary aspergillosis (ABPA), chronic obstructive pulmonary disease (COPD), and asthma.[4] However, there is a large population of patients with idiopathic bronchiectasis,[47] indicating that a specific etiology could not be identified and that could be related to other genetic factors.

In other respiratory diseases, it has also been described the role of microRNAs and the epigenetic signature, as both airway infection and inflammation can induce epigenetic changes, including histone acetylation and gene methylation, that modulate gene expression.[48,49] To date, no extensive data is available in patients with bronchiectasis. Therefore, future directions may be focused on genetic and epigenetic studies to improve the mechanistic insights into idiopathic bronchiectasis biology.

MICROBIOME

Understanding the contribution of airway infection to the pathophysiology of bronchiectasis is a critical step toward the prevention of disease progression. The traditional quantitative microbiological cultures can provide useful data in the assessment of treatment response. Novel analyses in bronchiectasis have revealed that the total airway bacterial load can classify patients depending on their response to antibiotic treatment, being the good responders to inhaled antibiotics for those patients with elevated airway bacterial load.[50] However, it is known that not only the bacteria quantity but also the diversity is important in airway diseases, and the latter one cannot be addressed by traditional microbiological techniques.

Current knowledge of lung microbial communities in bronchiectasis is increasing due to the use of next-generation sequencing techniques in lung samples. Microbiome studies have revealed that, as it has been reported in other airway diseases,[51] pulmonary dysbiosis is also observed in patients with bronchiectasis, being the most severe patients with the most important loss of bacterial diversity. Recent studies have also associated the pulmonary dysbiosis observed in bronchiectasis with inflammatory markers and with impaired respiratory function.[52]

However, future directions in bronchiectasis are focused on integrative microbiomics, which involves the multi-biome integration of bacterial, viral, and fungal communities. This novel approach called interactome has recently shown that patients at greatest risk of exacerbation have less complex microbial co-occurrence networks, reduced diversity, and a higher degree of antagonistic interactions in their airway microbiome.[53] The advantage of integrative microbiomics is that can detect the influence of microbial interactions in the exacerbation risk, whereas the analysis of

single microbial groups cannot address it. Further studies integrating network analyses to better understand the obtained results are needed to keep raising our knowledge toward the biology of the exacerbations in bronchiectasis.

OTHER RELEVANT OMICS

As airway diseases are complex and multifactorial, there is a need to integrate multiple aspects that may play a role in the prognosis of the disease. The available omics technologies also provide data about protein (proteomics), RNA expression (transcriptomics), metabolites (metabolomics), lipid mediators (lipidomic), and glycans level (glycomic).[54] Although few studies have been reported in bronchiectasis using these approaches, an increase in their application is expected in the next few years. Finch and colleagues reported a total of 80 proteins significantly associated with *P. aeruginosa* infection using sputum proteomic profiling in patients with bronchiectasis.[20] Among these proteins, the authors found for the first time in airway diseases that the increased levels of a protein called pregnancy zone protein (PZP) were associated with airway infection, disease severity, and NETs releasing. As the presence of NETs in bronchiectasis has been associated with the response to treatments, PZP would also participate in this response. Therefore, the main advantage of omics relies on the discovery of biomarkers not previously selected through targeted methods.

All these approaches are applied to the host but some of them, such as genomics and proteomics, have also been applied to bacteria to better understand the interaction between pathogens and the host immune response.[55] With the advances that genomics and microbiome have provided in bronchiectasis, it is tempting to consider that the other omics mentioned will also increase our knowledge about complex diseases in a near future. Therefore, further studies using these approaches are necessary to improve our understanding of the nature of bronchiectasis.

PERSONALIZED MEDICINE

The term precision or personalized medicine has been proposed to define treatments targeted to the needs of individual patients based on genetic, biomarker, phenotypic, or psychosocial characteristics, that distinguish a given patient from other patients with similar clinical presentations.[56] The main objective of precision medicine is to improve clinical outcomes for individual patients while minimizing unnecessary side effects for those likely to respond to a given treatment. In patients with bronchiectasis, the need for personalized treatment has been incentivized by the identification of patient endotypes based on several biomarkers.

As a way toward precision medicine of airway diseases, Agustí and cols introduced the concept of "treatable traits" arguing that the current airway disease diagnostic labels are imprecise, often overlap, and lead to empirical therapy with low clinical benefits. These authors proposed that a biomarker approach, based on the recognition of clinical phenotype and endotypes, can help to personalize treatment options and, consequently, may result in better clinical outcomes.[57,58] In bronchiectasis, a treatable trait approach has been proposed considering an etiologic, pulmonary, extrapulmonary, and environment/lifestyle approach to improve lung function, exercise capacity, and quality of life, decrease exacerbations and hospitalizations and increase survival.[59] This multimodality approach to treatment should impact in better clinical outcomes, but it is necessary to test in prospective studies. Identifying the frequency and clinical impact of individual treatable traits, their biological basis, and the best way to address them will be relevant research lines in the near future.

Recent progress in understanding endotypes has permitted the development of new therapies in bronchiectasis, specially targeting neutrophilic inflammation.[60] Neutrophils are the dominant inflammatory cells in the airway of most patients with bronchiectasis, and it is well known that increased levels of neutrophil-derived products (eg, NE and metalloproteases) are associated with poor clinical outcomes.[17,24] The inhibition of these products is, therefore, a logical approach to precision medicine for these patients. A recent study has shown that Brensocatib, an inhibitor of dipeptidyl peptidase 1 (DPP-1), the enzyme responsible for the activation of neutrophil serine proteases, has been associated with better clinical outcomes in phase 2 clinical trial.[61] In this study, patients with bronchiectasis who received active treatment experienced increased time to first exacerbations, decreased frequency of severe exacerbations, and a slower decline in lung function, while sputum NE activity was reduced during all treatment periods. Furthermore, Brensocatib also blocks the activation of other proteases stored in neutrophil granules, consequently reducing the whole neutrophil serine proteases content in the airways. All in all, the main advantage of this approach is that the inhibition of DPP-1 allows the necessary migration of neutrophils during bacterial infection while controlling their excessive activation to avoid tissue damage. Overall, irrespective of the promising results of these early studies, larger phase III studies

are needed to evaluate the potential clinics' efficacy of those treatments.

Other several treatments are under study to reduce airway proteases activity in patients with bronchiectasis. Molecules to inhibit NE activity directly or additional DPP-1 inhibitors have been developed in recent years, and different clinical trials are underway or will start soon.[60] The results of these studies will bring new opportunities for research for the next years. In addition, the study of new pathogenic pathways, mainly related to airway inflammation and ciliary dysfunction, will be necessary to lead to many new therapeutic opportunities. For that purpose, personalized medicine is required, and it will only be achieved by the development of biomarkers and the use of stratification tools that can be applied in clinical practice.[62]

SUMMARY

Emerging evidence suggests that endotypes exist in the bronchiectasis population. For that reason, bronchiectasis treatment is challenging, and many recent randomized controlled trials have failed to prove any clinical improvement. In the era of multi-omics approaches, there is an urgent need to generate data to better stratify patients in endotypes for the development of personalized medicine. The integration of multiple aspects into systems biology studies, such as genomics, microbiome, transcriptomics, proteomics, metabolomics, lipidomics, and glycomics, generate a more comprehensive understanding rather than analysis using single variables and individual outcomes. In this line, the Bronchiectasis Research Involving Databases, Genomics and Endotyping (BRIDGE), an EMBARC 2 Study (www.clinicaltrials.gov/NCT03791086) is an observational cohort study that aims to identify and characterize subpopulations of patients with bronchiectasis, during periods of stability and exacerbation, and to link these with meaningful clinical outcomes. Therefore, the stratification of patients with bronchiectasis according to endotypes will be pivotal in the development of successful clinical trials to treat the right patients with the right intervention at the right time.

CLINICS CARE POINTS

- Clinical and biological heterogeneity is the main cause of clinical trial failures in bronchiectasis.
- Research focused on the identification of endotypes and treatable traits in bronchiectasis will help us to move toward the development of a personalized medicine.
- NE is currently the most promising biomarker and therapeutic target in bronchiectasis.
- Further studies applying omics technologies and integrating data in network analyses are needed to find new local and systemic biomarkers with potential application to the clinical practice.

DISCLOSURE

The authors have nothing to disclose.

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