

A narrative review of novel methods for diagnosing bronchiectasis

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Abstract

Bronchiectasis, a chronic respiratory condition, presents with a wide array of signs and symptoms that often overlap with other chronic lung diseases. Accurate diagnosis in both primary and secondary care settings is crucial. However, the heterogeneous nature of bronchiectasis complicates the diagnostic process. A “treatable traits” framework, considering endotypes, and biological features, may guide more individualized diagnosis. A broad range of assessments can help identify the underlying causes of bronchiectasis, as well as associated pulmonary, extrapulmonary, and environmental factors. Despite recent advances, such as novel imaging modalities, artificial intelligence-associated diagnostics and emerging biomarkers there remains a critical need for continued refinement and innovation in diagnostic methods.

Keywords

Bronchiectasis, chronic respiratory diseases, diagnosis

Introduction

Bronchiectasis is characterized clinically by persistent cough and sputum production, alongside abnormal thickening and dilation of the bronchial walls, observable through imaging.¹ The first descriptions of bronchiectasis date back to 1819 by René Laënnec through auscultation and autopsy findings,² and radiographic diagnosis became feasible with the introduction of contrast bronchography in 1922.³ In the 1950s, correlations between radiological and histopathological findings were firmly established.⁴

Historically underdiagnosed, bronchiectasis has seen a marked increase in incidence and prevalence over the past two decades. It now affects individuals across all age groups with considerable geographic variation.⁵ Seitz et al. reported an annual increase of 8.7 percentage in bronchiectasis diagnoses among the United States Medicare population from 2000 to 2007.⁶ In 2018, Henkle et al. analyzing multiple insurance databases, estimated a prevalence of 701 cases per 100,000 individuals, higher among women and older adults.⁷ Comparable or higher rates have been reported in the United Kingdom, Germany, Spain, Singapore, and China.⁸⁻¹² The socioeconomic impact of the disease has been on the rise.¹³ This increase is attributed partly to greater disease awareness and the wider use of computed tomography (CT) imaging. As well as a rising burden of underlying causes.⁸

Bronchiectasis may present as a primary respiratory disease or as a complication of other

conditions such as asthma and chronic obstructive pulmonary disease (COPD). Given its multifactorial origins, early recognition across all healthcare specialties is vital to initiating appropriate management and improving patient outcomes. This review explores recent advances and emerging techniques in the diagnosis of bronchiectasis.

Recent advances in bronchiectasis diagnosis

Historically, the diagnostic landscape of bronchiectasis has been hampered by inconsistent disease definitions and a lack of standardized classification. This heterogeneity has posed significant challenges in clinical research and practice. In recent years, efforts have been made to categorize radiological and clinical features using unified diagnostic criteria to facilitate more precise disease recognition.^{14,15} High-resolution computed tomography (HRCT) remains the diagnostic gold standard for bronchiectasis, allowing detailed visualization of airway dilatation, wall thickening, and associated structural abnormalities. However, HRCT has limitations in functional assessment and may be less sensitive in detecting subtle changes in airway and vascular architecture. Low-dose helical CT, particularly at 40 mA, has been shown to outperform HRCT in certain diagnostic scenarios, offering a favorable balance between image quality and radiation exposure.¹⁶

With the advancement of new technologies in the medical world, artificial intelligence-based

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techniques for assessing and diagnosing bronchiectasis have been developed. One of the most important factors in the assessment of bronchiectasis is the arterial-to-airway ratio (AAR), which the CT can commonly assess, however, it has limitations such as limited area assessment and time-consuming. This index can be assessed with artificial intelligence-based techniques with greater speed and accuracy and at lower cost.^{17,18}

The use of AI-based methods plays an important role in reducing patient and clinician exposure, especially for younger patients. These techniques have been considered in addition to bronchiectasis, in primary ciliary dyskinesia (PCD) and cystic fibrosis (CF). It has been shown that the use of low-dose CT in the volumetric evaluation of CF patients minimizes radiation exposure. Magnetic resonance imaging (MRI), though less widely adopted, is emerging as a complementary tool for evaluating pulmonary function and perfusion in bronchiectasis, particularly in pediatric populations or cases requiring serial imaging.¹⁹ Despite promising applications, comparative data on the diagnostic performance of MRI versus CT in bronchiectasis remain limited, warranting further investigation.

Today, the assessment and diagnosis of PCD methods including nasal nitric oxide testing, electron microscopy, and high-speed camera microscopy are recommended by the American Thoracic Society (ATS) and the European Respiratory Society (ERS).²⁰⁻²³ In addition, methods such as cell culture and immunofluorescence are used to differentiate PCD from its more advanced stages.²⁴ The use of these techniques is limited due to their high cost, unavailability in many medical centers, and the need for high expertise and extensive experience in algorithm development.²⁵ To overcome these limitations, an alternative standardized and optimized method is needed to accurately assess and diagnose PCD.

Diagnosing inflammation and severity of bronchiectasis using biomarkers

Chronic neutrophilic inflammation is a hallmark of bronchiectasis and a key driver of its progression. Persistent inflammation contributes to recurrent infections, mucus hypersecretion, airway remodeling, and ultimately, irreversible lung damage. Identification of specific clinical phenotypes and "treatable traits" is critical to guiding individualized management strategies.²⁶ Among the most studied biomarkers is neutrophil elastase (NE), a proteolytic enzyme released from azurophilic granules during neutrophil degranulation. NE contributes to tissue destruction, increased mucus production, and impaired mucociliary clearance. NE activity, measurable in sputum, correlates with disease severity, extent of radiological involvement, spirometry decline, and mortality. Elevated NE levels are particularly associated with chronic infection by *Pseudomonas aeruginosa*, and antibiotic treatment has been shown to reduce NE concentrations.^{26-29 29-31} Given its prognostic value, NE is considered a central biomarker for bronchiectasis.

In addition, other biomarkers have been introduced for the evaluation of bronchiectasis. Examples of these biomarkers are mucins MUC2, MUC5AC, and MUC5B, which are observed in sputum samples of bronchiectasis patients. Studies have shown that the increase in these glycoproteins is one of the main effective markers of airway infection. One of the methods of bronchiectasis treatment is to control and reduce these mucins.^{29,32,33}

Another example of an effective inflammatory biomarker in the evaluation of bronchiectasis is extracellular traps in neutrophils (NETs). These markers are actually a set of cellular components such as histones, DNA strands, and antibacterial proteins that are released from neutrophils in response to pathogens. Studies have shown that the examination of NETs can be effective in controlling inflammation and airway obstruction in bronchiectasis. It is also effective as a key factor in assessing the severity of the disease and assessing the response to treatment.^{25,34,35}

Antimicrobial agents such as SLPI, secretory leukocyte protease inhibitor, and proinflammatory factors such as lactoferrin, human cathelicidin peptide LL-37, and lysozyme can be associated with disease phenotype and the likelihood of exacerbation.^{29,34,35} Although bacterial load is not recognized as a biomarker in disease pathogenesis, it can reflect levels of inflammation and disease severity and may be useful in predicting response to treatment.²⁹

Other biomarkers, such as matrix metalloproteinases, have been identified that can be effective in assessing the severity and level of inflammation caused by bronchiectasis, however, understanding their function requires further studies.³⁶⁻³⁹

Endotypes of bronchiectasis

Bronchiectasis is a highly heterogeneous condition, and a one-size-fits-all approach to diagnosis and treatment is often inadequate. To improve clinical management, there has been increasing interest in stratifying patients based on underlying biological mechanisms, so-called endotypes. Defining bronchiectasis endotypes can help tailor therapies to specific subgroups and improve clinical outcomes. One of the most common ways to classify endotypes is by the underlying etiology of the disease. This includes post-infectious bronchiectasis, immunodeficiency-related bronchiectasis, allergic bronchopulmonary aspergillosis (ABPA), primary ciliary dyskinesia (PCD), cystic fibrosis (CF), and bronchiectasis associated with autoimmune or connective tissue diseases. Identifying the causative condition is critical, as it may dictate both treatment strategies and prognosis (Table 1).⁴⁰ Another emerging approach involves categorizing patients based on inflammatory patterns, typically neutrophilic or eosinophilic inflammation. While neutrophilic inflammation dominates in the majority of patients and is associated with persistent bacterial colonization (especially *Pseudomonas aeruginosa*), a subset of patients exhibits eosinophilic inflammation, which may overlap with asthma or respond to inhaled corticosteroids and biologics.

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Comorbidities or underlying causes	Clinical features	Underlying biological features
COPD	Smoking historyAirflow obstruction	Endotypes based on proteome and microbiome.
Asthma	Most frequent BE-associated comorbiditiesBronchial hyperresponsivenessVariable airflow obstructionFrequent exacerbationsHeterogenous disease with multiple endotypes	Th2-driven inflammation or less commonly neutrophilic.
GORD	Frequent exacerbationsGreater radiological extentPulmonary microaspirationGram-negative pathogens	Neutrophilic inflammationProteobacteria dysbiosis.
IBD	Large airway involvementLarge sputum volumesNegative sputum culturesFemale gender	A shared lymphocytic inflammation between lungs and gut.
Primary immunodeficiency	Infections since childhoodUnderdiagnosed causeMost commonly CVID	Multiple genes involvedNeutrophilic inflammation.
Secondary immunodeficiency	Infections with onset at any ageUnderdiagnosed cause	Iatrogenic immunosuppressionAutoimmune mechanisms
Systemic autoimmune diseases	Rapidly progressive diseaseFrequent exacerbationsPrevalence of 20% in RA patients and from 7% to 54% in Sjögren syndrome	Autoimmune featuresHigh risk of infections due to immunomodulating therapy
PCD	Underdiagnosed causeEarly age of onsetHeterogeneous diseaseChronic rhinosinusitisCongenital cardiac defectsOtitis media	Multiple genes involved (DNAH5 most frequent defect)Neutrophilic inflammation
AATd	Panlobular emphysema in lower lobesEarly onsetFrequent exacerbations	Abnormal AAT genotypesNeutrophilic inflammation
Allergic bronchopulmonary aspergillosis	WheezingMucus plugging	Elevated IgEEosinophilic inflammation
Non-tuberculous mycobacterial infection	Slowly progressive dyspneaWeight loss	ImmunosuppressionImpaired mucociliary clearance

Neutrophilic inflammation is more prevalent in bronchiectasis. NETs are one of the therapeutic responses to combat various pathogenic microorganisms. In bronchiectasis patients, excessive production of these factors causes inflammation and tissue damage. Enzymes derived from NETs have negative consequences such as impaired response to bacterial agents, tissue degranulation, and increased mucus.³⁶ Paying attention to these factors as a prognosis can be effective in developing treatment plans at different levels of bronchiectasis.

The similarity of clinical features of bronchiectasis with chronic obstructive pulmonary disease (COPD) has led to patients with this manifestation being commonly referred to as COPD-Bronchiectasis Association. However, it has been shown that the lung microbiome profile of these patients differs from that of COPD patients, leading to different treatment responses.⁴¹ Considering this clinical similarity, patients with bronchiectasis, COPD, and COPD-Bronchiectasis Association are divided into 5 endotypes based on sputum microbiome and clinical features, each requiring its own specific treatment.

The first endotype has been proposed as diverse-protective. The second endotype is caused by *Haemophilus* infection and is controlled by tetracyclines. This subgroup is called *Haemophilus*-proteolytic. The third type is patients who have Gram-negative bacterial infection and exhibit

features of bronchiectasis. This group is called infected-epithelial and is indicated by macrolide therapy. The fourth type, which is treated with macrolides and is characterized by excessive neutrophil activity and increased NET production, is proteobacteria-neutrophil. The fifth endotype is Th2, and inflammation control in this condition is possible with inhaled corticosteroids (ICS).^{42,43}

Microbiome in bronchiectasis patients

The microbiome is a collection of genetic information from various microorganisms in the body.⁴⁴ Under different conditions, the steady state of homeostasis of the body depends on the actions and reactions of the microbiome of different areas.⁴⁵

It has been shown that many inflammatory pathways and the severity or weakness of respiratory diseases are influenced by the respiratory tract microbiome.⁴⁶ Some models have proposed a cycle influenced by the respiratory tract microbiome, including a set of mechanisms of inflammation, infection, colonization of microorganisms and inadequate mucociliary clearance, which are effective in the occurrence and severity of bronchiectasis.⁴⁷⁻⁴⁹

The microbiome of a healthy person often includes benign microorganisms such as *Protella*, *Streptococcus* and *Villonella*.⁵⁰ This microbiome complex helps maintain immune homeostasis

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with a Th17 response.⁵¹ Haemophilus, Villonella and Pseudomonas microorganisms are often observed in increased numbers in the microbiome of bronchiectasis patients.⁵² These pathogens, along with the stimulation of immune disorders in the airways, contribute to the exacerbation of the disease.⁵³ The microbiome varies among bronchiectasis patients and is usually stable across disease phases.^{54,55}

Lower bacterial diversity has been shown to be associated with greater disease severity, impaired respiratory function, increased exacerbation rates, and increased mortality.^{54,57} In contrast, higher bacterial diversity is associated with reduced inflammatory cytokines and improved patient outcomes.^{56,57} In patients with bronchiectasis, the microbiota of Haemophilus and Pseudomonas interact, and their increases are associated with disease severity due to increased inflammatory markers.^{53,55}

In bronchiectasis patients, in addition to the aforementioned microorganisms, fungi such as Cryptococcus, Aspergillus, and Clavispora are also found, which play a significant role in the pathogenesis of the disease. Few studies have been conducted in this field so far. However, it seems that the increase in Aspergillus is more pronounced in the exacerbation of the disease.⁵⁸ In addition, viruses such as some adenoviruses, rhinovirus, influenza A and B, and human T-lymphotropic virus-1

are found in abundance in different periods of bronchiectasis.^{59,60} It seems that the stability of the microbiome is achieved with the help of bacteriophage viruses.

The role of antibiotics in the interactions of microbial networks is significant. This mechanism can be explained by the effect of antibiotics on the interactome and the effect on resistant pathogens.^{51,62} Recently, the concept of multibiome has been proposed as an integrated microbial community that can identify potential risks and suboptimal approaches by considering the set of interactions of different microorganisms. Also, the study of the interactome plays a significant role in evaluating multibiome interactions and predicting therapeutic responses to adopt the most effective therapeutic approach.^{63,64}

Conclusion

The clinical presentation of bronchiectasis is varied, typically featuring a chronic cough that can occur in patients regardless of age or gender. Future efforts should aim to establish more efficient diagnostic methods and to improve treatment algorithms for individuals diagnosed with bronchiectasis.

Declaration of competing interests

Nothing to declare

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