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REVIEW

The Etiological Screening of Bronchiectasis

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ABSTRACT

Bronchiectasis was once considered to be the manifestation of other diseases, but this topic is gaining growing interest due to its increase in incidence and prevalence. Bronchiectasis is characterized by a combination of clinical and radiological features, but we still lack a full understanding of their pathophysiological mechanisms. They are often present in patients affected by cystic fibrosis and therefore the exclusion of this disease is of paramount importance in patients affected by bronchiectasis.

The most recent guidelines, mostly based on expert opinions, state that all individuals with bronchiectasis should undergo a minimum bundle of tests which should be tailored to each patient. The determination of the etiology of bronchiectasis can guide treatment and influence prognosis.

The next step in this field of research is the standardization of etiological screening of bronchiectasis that would allow optimal patient management and the optimization of the available resources.

Keywords: Bronchiectasis. Etiological screening. Treatable traits.

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DEFINITION OF BRONCHIECTASIS

Bronchiectasis is a chronic respiratory disease identified by a combination of radiological and clinical elements. The gold standard diagnostic technique consists in a high-resolution chest computed tomography (CT) scan to detect abnormal dilations of the bronchial tree. Recent studies describe the exact radiological criteria that increase the confidence in bronchiectasis diagnosis: an inner or outer airway–artery diameter ratio of 1.5 or more, lack of airways tapering and visibility of the airways in the periphery[1].

The combination of at least one of these bronchiectasis-defining findings on CT accompanied by clinical signs and symptoms of the disease allows the diagnosis of bronchiectasis. As far as the clinical elements are concerned, at least two among the triad are required: cough most days of the week, sputum production most days of the week, or a history of exacerbations[1].

In the past, bronchiectasis was considered the feature of other more studied and well-known diseases, in particular of cystic fibrosis (CF). Bronchiectasis not related to dysfunctions of the cystic fibrosis transmembrane conductance regulator (CFTR) channel has suffered from the lack of a proper "disease – identity", being simply defined as what it is not. Unfortunately, this approach led to a neglect of research on specific mechanisms that are responsible for bronchiectasis development and progression[2].

Only in recent years, the focus was put on bronchiectasis as a self-standing clinical entity and the unmet need of etiological investigation emerged. One of the main drivers of this process is the increase in both prevalence and incidence of bronchiectasis across countries.

Recent European data describe an increase in the prevalence of about 40% in the last 10 years, especially in older females, while the prevalence in the USA has been estimated to be 52 per 100,000 people[3,4].

For what concerns Italy, a study published in 2020 describes how bronchiectasis prevalence has increased in the period spanning from 2005 to 2015 and confirms a female predominance. Together with gender, also aging is a major element correlated with an increase in bronchiectasis prevalence, especially older than 75 years of age; the highest prevalence was found in patients between 75 and 84 years of age and it reached up to 46.7 and 40.0 per 100,000 person-years in men and women, respectively[5].

This new data helped shift the previous consideration of bronchiectasis as an orphan disease towards the awareness of a more common disease[6].

WHEN AND HOW TO EXCLUDE CYSTIC FIBROSIS

Cystic Fibrosis is the most common life-limiting genetic disease in the Caucasian population. It is caused by at least two mutations affecting the CFTR gene encoding for a transmembrane chloride channel responsible for the regulation of liquid volume on epithelial cell membranes[7].

The relevance of excluding CF in adults with bronchiectasis is based on clinical, social-economical and psychological considerations. From a clinical point of view, both respiratory and

extra-respiratory manifestations in CF might benefit from a multidisciplinary approach in highly specialized referral centers. Moreover, patients with CF have access to CF-specific treatments, as in the case of inhaled antibiotics and new CFTR modulators. This clinical management has been reported to have a favorable impact on long-term clinical outcomes and quality of life. From a social-economical point of view, patients with CF might have access to free care in some countries or benefit from dedicated legislation or health insurance plans. From a psychological point of view, CF can be interpreted as a chronic, life-limiting condition with relevant implications in terms of patients' life plans. However, testing for CF is not included in the minimum bundle of etiological investigation for bronchiectasis as recommended by most national and international guidelines, and the exclusion of CF is suggested only in the presence of specific clinical features[8].

It is worthy to note that CF testing lacks a standardized approach in adults with bronchiectasis, and a reliable determination is not always feasible[9]. While most patients with CF are identified at birth or during the first years of life, late diagnosis during adulthood is not infrequent, especially in the case of non-typical clinical manifestations. Several limitations for CF testing have been reported in the adult population. Sweat test intermediate determinations might result from either impaired CFTR function, environmental factors, or test variability. Moreover, in previous reports, sweat chloride concentrations appeared to increase during life and no threshold for normal chloride concentration in sweat has been validated for the elderly population[10]. Second, the accuracy of gene analysis might vary according to different diagnostic strategies: the use of CFTR panels that are empowered to test only for CF-causing mutations leads to high specificity but low sensitivity of the findings.

Third, electrophysiological tests, including nasal potential difference, might be limited by a relevant inter- and intra-operator variability, and the need of highly trained staff affects the spread of these methods across centers[11].

THE RELEVANCE OF THE ETIOLOGICAL INVESTIGATION

The importance to determine the cause of bronchiectasis is even stronger under the light that specific etiologies might deserve proper clinical management, and that missed or delayed diagnosis might lead to worse clinical outcomes. This is clearly depicted by a European cohort study published in 2015 that indicates that an etiology of bronchiectasis can be determined in 60% of patients, and that this can change the management of patients in 13% of cases[12].

A broad spectrum of diagnostic tests is necessary to investigate the etiology of bronchiectasis focusing both on pulmonary and extrapulmonary features. The diagnostic flowchart should be tailored to each patient depending on their clinical manifestations and the site of care (e.g., primary, secondary, and tertiary care) to optimize patient management[13].

First, the identification of some bronchiectasis etiologies might grant access to specific treatments of the underlying condition that can slow down or stop the disease progression. This is

the case of the augmentation therapy for alpha-1 anti-trypsin deficiency (AATD) and IV immunoglobulins for immunodeficiencies. An example of this are patients affected by AATD in whom intravenous infusion of alpha1-proteinase inhibitor, especially in patients with moderate obstructive syndrome, can increase AAT levels, slow the progression of emphysema, reduce exacerbation frequency and improve patients' quality of life[14].

Second, bronchiectasis can be the pulmonary manifestation of a systemic disease. This leads to the need to identify and treat also extra-pulmonary symptoms that might impact patient-reported outcomes, as in the case of CF and primary ciliary dyskinesia (PCD). Both these diseases are systemic diseases with major, but not exclusive, pulmonary manifestations. A proper diagnosis would allow the treatment of the other symptoms ranging from chronic rhinosinusitis to otitis media and fertility counselling[15].

It is also worthy to note that some underlying systemic conditions, as CF, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis (RA), if not addressed, might affect long-term clinical outcome, including mortality. The need for an etiological workup in bronchiectasis is necessary also to understand if there are, and which are, the etiological elements responsible for a more severe clinical manifestation of the disease. It was proved that there are no specific etiologies associated with a more severe outcome and, rather, that all patients deserve a full diagnostic workup that is not influenced by the severity of the disease, but rather that aims at detecting all possible treatable causes of the disease[12].

Exceptions to this are COPD and RA, which have been found to be commonly associated with bronchiectasis with poor outcomes. In particular, patients with bronchiectasis associated with COPD were found to have a higher prevalence of *Pseudomonas aeruginosa* infections, more frequent hospital admission and higher mortality (28% in 4 years). Higher mortality was described also in patients affected by bronchiectasis and RA. Therefore, these patients should undergo more frequent follow-up visits and stricter monitoring[16]. Bronchiectasis has been described as a possible complication of RA and this has particular relevance in case of concomitant *Aspergillus* colonization; in this case, immunosuppressive treatment increases the risk of a more invasive fungal diseases[17].

Lastly, bronchiectasis can also be the manifestation of hereditary conditions demanding a prompt referral to genetic counseling in order to assess and prevent the risk of transmission, as in the case of CF, PCD and AATD[18].

THE CURRENT RECOMMENDATIONS FOR ETIOLOGICAL INVESTIGATION IN BRONCHIECTASIS

Over the past period, several expert groups issued recommendations on the clinical management of adults with bronchiectasis, including the etiological screening[19-22].

First-level investigations in combination with specific algorithms have been proposed to increase the probability of finding a cause of bronchiectasis with the better allocation of healthcare costs[23].

In 2017, Polverino et al.[24] published the first international guidelines on bronchiectasis by the European Respiratory Society (ERS) and provided indications on the etiological screening, mostly based on expert opinion, and not yet validated in prospective clinical studies. According to the authors, all adults with clinically significant bronchiectasis should undergo a minimum bundle of tests, including differential white cell count, serum immunoglobulins (total IgG, IgA, IgM), testing for allergic bronchopulmonary aspergillosis (ABPA) and simple spirometry with bronchodilation test. The rationale behind this approach is to provide inexpensive and readily available tests to detect both frequent conditions, as COPD-associated bronchiectasis, by the mean of a simple spirometry; and rare causes of bronchiectasis, as primitive or secondary immunodeficiencies, but with a significant impact on patient management.

Testing for ABPA includes determining total serum IgE, specific IgG and IgE for *Aspergillus*. Although this etiology is supposed to be frequent and treatable, it might be limited by the lack of specific criteria for the diagnosis of ABPA in patients with bronchiectasis compared to the general population and the heterogeneity in incidence depending on geographical variability. Both COPD and bronchiectasis are considered risk factors for the occurrence of *Aspergillus*-associated disease. Modern molecular technologies allow better detection and identification of the mycobiome that characterizes the airways, and the understanding of how it changes in cases of respiratory pathologies would provide clinicians with another tool to understand the pathophysiological mechanism of bronchiectasis[25].

Present knowledge considers a double possible interpretation of the association between bronchiectasis and fungal, more specifically *Aspergillus*, colonization: the first model considers *Aspergillus* to be the element that, once present in the healthy lungs, is responsible for initiating the airway damage that eventually leads to their abnormal dilation, while the second model considers patients already affected by bronchiectasis to be a susceptible host for subsequent *Aspergillus* colonization. These two models are not necessarily mutually exclusive[17].

At this level the major pros would be: 1) the detection of the most common treatable etiologies; 2) the availability of this investigation in both primary and secondary care; 3) the relatively low cost of these examinations. On the other hand, physicians following this approach might be aware of the possibility that their patients might have other identifiable etiologies of bronchiectasis they are missing.

According to the ERS document, second-level investigations should be individualized according to clinical and/or radiological features. In the case of persistent sputum production since childhood, *situs* abnormalities, congenital cardiac defects, nasal polyposis and/or chronic rhinosinusitis, chronic middle ear disease, a history of neonatal respiratory distress or neonatal intensive care admittance, screening for PCD with nasal nitric oxide assay should be considered. In case of suspected connective tissue disease, the patient should be prescribed autoantibodies screening, focusing on serum levels of antinuclear autoantibodies, extractable nuclear antigen antibodies, antineutrophil cytoplasmic antibodies, and anti-cyclic citrullinated peptide antibody.

Chronic sinusopathy should be investigated *via* a facial CT scan and otolaryngological specialist evaluation.

Gastro-esophageal reflux disease (GERD) should be investigated and treated in case of poorly controlled symptoms.

A group of investigations, including genetic analysis and further investigations for PCD and CF, can be highly costly both in terms of economic resources and dedicated trained staff and time and might be considered in specific tertiary care centers.

LIMITATIONS IN UNDERSTANDING THE ETIOLOGIES OF BRONCHIECTASIS

Our current understanding of bronchiectasis etiologies mainly relies on registries. Gao et al.[26] have extensively investigated this topic in more than 50 studies enrolling up to 8,000 adults across more than 20 different countries. According to this study, the underlying cause of bronchiectasis can be identified in nearly half of the included patients (55.2% of 8,608 patients)[26]. In Gao's study, post-infective bronchiectasis accounts for up to 30% of cases, while a 2021 study shows that bronchiectasis with post-infective etiology range from 14 to 17% of all cases and are second only to idiopathic bronchiectasis[23].

However, there is no consensus on the criteria (neither in terms of severity nor of infection type) needed to define a pulmonary infection as a potential risk factor for bronchiectasis development.

Of all the other conditions associated with bronchiectasis, each responsible for less than 5% of cases, the most common are immunodeficiencies[27].

As Gao and colleagues noted[26], there were significant differences in the etiologic *spectra* among bronchiectasis patients according to different geographical regions: within the post-infective group, post-tuberculosis (TB) seems to be the predominant category, but this *datum* largely depends on the country under analysis: TB seems to be responsible for up to 62.5% of all bronchiectasis in Africa, while for 31.2% cases in Europe and 18.9% in North America[12].

The reason for this disparity is unclear but might be associated with different factors including different patient populations assessed, the varying number of the available studies and the individual study variation.

The etiological screening of bronchiectasis is an ongoing process that is still affected by several factors[12]. Most of the studies on this topic have a retrospective design without clear information neither on the number nor on the type of etiological investigations performed. This approach led to a selection bias in terms of both an overestimation of the proportion of patients with specific etiologies and a large use of the 'idiopathic' definition, especially in the presence of a poor etiological workup.

The lack of an animal model and of basic research is a relevant unmet need affecting the understanding of the pathophysiological mechanisms of the disease[12]. An example is the association between bronchiectasis and some reported etiologies such as inflammatory bowel diseases (IBD) and RA. This

association has been well documented by epidemiological studies and, in the context of IBD, a close temporal relationship between curative colectomy and diagnosis of bronchiectasis is well established[28]. However, we still lack a deep analysis of possible underlying mechanisms.

Furthermore, it is unclear whether a suspected etiology of bronchiectasis actually precedes or rather comes after the development of the disease. In some diseases, as CF or post-TB bronchiectasis, it seems reasonable that bronchial dilations, allowing secretions to accumulate, provide a medium for non-tuberculous mycobacteria (NTM) colonization and proliferation. However, pulmonary NTM lesions can cause cartilage and smooth muscle destruction, therefore precede and contribute to the subsequent development of bronchiectasis. This topic was studied in detail: Okumura et al.[29] described the case of a patient in which pulmonary lesions by *Mycobacterium avium* complex (MAC) seemed to precede the central bronchial lesion leading to subsequent development of bronchiectasis. Fujita et al.[30] evaluated pathological abnormalities in a case series of resected bronchiectasic lung due to NTM disease and assumed that destruction of cartilage and smooth muscle layer as well as granuloma formation were caused by MAC and could finally lead to bronchiectasis. Undoubtedly, bronchiectasis and NTM lung disease are connected: NTM are isolated in 12% of adult patients with bronchiectasis, while a specific diagnosis of pulmonary NTM disease requiring treatment is reached in 8.8% of them. A coinfection of MAC and other bacteria is present in the majority of the patients (66%), *P. aeruginosa* is present in almost one third of them[31].

Bronchiectasis, chronic lung diseases, pulmonary fibrosis, and decreased lung immunity are some of the known risk factors for pulmonary NTM diseases. Better molecular tools for rapid diagnosis of NTM, understanding of immunopathogenesis, and host pathogen interactions are needed[32].

The accuracy of etiological screening is also affected by the well-known delay between the onset of symptoms and bronchiectasis diagnosis. The identification of the etiology of bronchiectasis in the presence of a recall bias" is typical of post-infective bronchiectasis which might have an underlying cause, an infection that occurred during infancy or adolescence and that is not remembered by the patient unless it is well clinically documented. A landmark study by Shoemark et al.[18] demonstrated a significant delay between onset of bronchiectasis symptoms (average age: seven years), and the radiological diagnosis of bronchiectasis (average age: 49 years). This temporal distance might be responsible for the inability of many patients to properly remember clinical information if not well documented.

The co-existence of bronchiectasis and other obstructive respiratory diseases, as COPD and asthma, is a further relevant challenge in the etiological investigation.

The diagnostic approach to bronchiectasis is, therefore, challenging, especially considering that bronchiectasis-related signs and symptoms may overlap with other chronic respiratory diseases[13].

As previously stated, bronchiectasis is a clinical and radiological diagnosis associated with

cough, sputum production and recurrent respiratory infections. The clinical presentation inevitably overlaps with other respiratory disorders such as asthma and COPD. In addition, the majority of patients with severe COPD and up to 30% of asthmatic patients, if the disease is not well controlled, also have bronchiectasis on CT. Co-diagnosis of bronchiectasis with another airway disease is associated with increased lung inflammation, frequent exacerbations, worse lung function and higher mortality[33].

This led to the hypothesis of overlapping syndromes, the most studied of which is bronchiectasis-COPD (BCOS)[33]. However, this clinical entity is still waiting for a proper clinical validation.

CONCLUSIONS AND FUTURE STEPS

In the clinical management of patients with bronchiectasis, the standardization of etiological screening is still a challenge, and international recommendations mainly rely upon the opinion of experts. However, in the light of the beneficial impact on patients' outcomes, the identification of treatable conditions is warranted. We suggest both a proactive case finding of bronchiectasis at primary level, as well as a systematic approach to etiological investigations depending on medical expertise on bronchiectasis, healthcare setting and patient severity of the disease.

In the case of complex patients, it could be useful to organize hub centers capable of advanced screening tests in order to ensure the etiological diagnosis and the best clinical management.

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Dr Amati received consulting fees from Zambon, Chiesi and INSMED.

Dr Gramegna received consulting fees from Zambon, Grifols, Chiesi, INSMED, and Vertex, and has particpated in the board for Vertex and Lega Italiana Fibrosi Cistica.

Dr Leonardi has nothing to disclose.

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