Phenotyping in bronchiectasis: Are we moving toward a personalized medicine?

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ABSTRACT

Bronchiectasis (BE) is a heterogeneous disease. Similarly, to other chronic airway diseases, such as asthma and chronic obstructive pulmonary disease, management of BE patients requires a specific and personalized treatment that depends on many clinical, functional, and microbiological variables. Therefore, developing phenotyping methods that can help clinical and therapeutic choices is of paramount importance. Various methodological approaches have been used to personalize patients’ management. In this review, we explore the main tools identified so far to classify and phenotype BE patients, including the approaches based on BE etiologies, disease severity, cluster analysis, and endotyping. We also discuss the strengths and limitations of every approach and highlight the similarities and differences between these studies. Finally, we review the therapeutic implications and clinical management connected with each approach.

Key words: Bronchiectasis, etiology, severity, inhaled antibiotics, phenotyping

INTRODUCTION

Bronchiectasis (BE) is a chronic disease of the airways characterized by irreversible dilation of the bronchi. These alterations lead to the impairment of mucociliary clearance and the onset of a vicious circle with persistent bacterial colonization, chronic inflammation, and progressive tissue destruction.¹ Despite the paucity of data regarding BE prevalence worldwide, a recent population-based study showed that BE is far from being defined a rare disease.² BE represents the outcome of a wide group of etiological factors, with patients sharing different clinical manifestations, responses to treatment, and clinical outcomes.³ In daily clinical practice, the spectrum of the disease can move from mild disease with limited clinical and radiological
impairment to more severe disease with disseminated pulmonary involvement, severe functional impairment, chronic airways infection by difficult-to-treat pathogens, and frequent exacerbations.

Between these two extreme scenarios, a wide range of clinical syndromes might exist, implying a tailored management approach. So far, there are no specific indications for tailored treatment for BE patients. Over the past few years, several research groups tried to identify a tool to either stratify or cluster BE patients to detect specific groups that might respond to different treatments. In the recent past, studies with a similar aim conducted in other respiratory conditions, including chronic obstructive pulmonary disease (COPD) and asthma, have led to more personalized medicine approaches.

The aim of this review is to evaluate the current literature using various approaches to classify BE patients, with special attention to their clinical aspects and therapeutic perspectives.

**AN ETIOLOGY-BASED APPROACH**

The most common etiologies of BE include previous severe respiratory infections (e.g., bacterial pneumonia or tuberculosis), allergic bronchopulmonary aspergillosis (ABPA), impairment of ciliary clearance (e.g., primary ciliary dyskinesia), immunodeficiencies (e.g., hypogammaglobulinemia), and other airway diseases, such as COPD and severe asthma. However, there are many strengths and limitations related to this approach. The identification of treatable causes of BE may prevent the evolution of the disease, and international guidelines recommend to detect them. However, the etiology of BE leading to targeted therapy is only identified in a minority of cases. This reflects that idiopathic and postinfectious etiologies generally account for 50–70% of all cases in many case series. There is no agreement on the minimum bundle of tests to be performed to identify BE etiology, and recommendations of the international guidelines are not met in real life. Several etiologies have been associated with BE, but the real “cause–effect” relationships have been proved only in a few cases. Typical examples are the association between BE and nontuberculous mycobacteria (NTM) or ABPA where the “chicken-and-the egg” story might occur. Both NTM and ABPA might either predispose to the development of BE or colonize a BE lung. Furthermore, identification of some etiologies of BE, such as the “postinfective” one, suffers significant recall bias related to the difficulties in collecting information on a low respiratory tract infection episode occurred several years before. Finally, no good evidence has been published so far concerning the causality in the association/overlap between BE and obstructive diseases such as asthma and COPD.

According to a recent meta-analysis on the BE etiology, the idiopathic etiology was found in an average of 44.8% cases, with a high interstudy variability (range: 5–82%) depending on geographical and diagnostic differences. Apart from idiopathic BE, the other most common etiologies were postinfective (29.9%), immunodeficiency (5%), COPD (3.9%), and connective tissue disease (3.8%).

All of the latest international guidelines strongly recommend a comprehensive diagnostic workup, including a thorough medical history and baseline investigations, such as full blood count, major immunoglobulin classes, and serological tests for Aspergillus species. Furthermore, cultures of airway secretions are strongly recommended because they can detect pathogens, such as NTM. However, according to the meta-analysis published by Gao et al., the identification of the BE etiologies led to changes in patients’ management only in 18% of cases.

In a recent paper, Lonni et al. evaluated the possible correlation between BE etiologies and disease severity. No significant differences in the etiology of BE were found across different levels of disease severity, with the exception of a higher prevalence of COPD-related BE and a lower prevalence of idiopathic BE in patients with severe disease.

Few studies have evaluated patients’ phenotyping according to BE etiology. Buscot et al. performed a retrospective, single-center, university hospital-based study on 311 BE patients in Nice, France. They detected three phenotypes with distinct clinical, functional, and microbiological features: idiopathic, congenital, and COPD-associated BE. Anwar et al. identified two main groups: idiopathic BE and postinfection BE, with the latter being significantly younger at symptom onset compared to the former group. King et al., who collected data from 195 adult BE patients at a University Hospital in Melbourne, Australia, based their phenotyping on the disease onset. Patients with childhood onset, despite the younger age, showed higher disease severity and higher number of exacerbations.

**A SEVERITY-BASED APPROACH**

Another approach aimed to classify patients with BE is based on the degree of disease severity. BE severity, ranging from cases without symptoms or exacerbations to patients requiring lung transplantation, greatly impacts on patients’ management. Two recognized severity scores are the BE Severity Index (BSI) and the FACED score. They share some items, including age, pulmonary function tests (PFTs) with the forced expiratory volume in the in the 1st second (FEV1), presence of bacterial colonization, radiological extension, and the...
Table 1: Studies reporting bronchiectasis phenotyping according to bronchiectasis etiology and disease onset

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD-associated</td>
<td>Predominantly men, associated with tobacco use. Pts are older (median age 73 yrs), have more severe airway obstruction at diagnosis and P. aeruginosa is more frequently found in the sputum (65% of cases). Pts have a higher proportion of pulmonary hypertension (16% of cases).</td>
</tr>
<tr>
<td>Congenital</td>
<td>Younger pts at diagnosis (median age 20 yrs), lower rate of smoking (13%). Almost all of them (93%) have potential pathogens in their sputum (P. aeruginosa in 57% of cases, H. influenzae in 50%, and S. aureus in 36%). 40% underwent lobectomy.</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Mostly women, rarely smokers. Pts have better spirometry values at diagnosis and are less likely to carry P. aeruginosa (30% of cases).</td>
</tr>
<tr>
<td>Anwar et al. 2013[8]</td>
<td>Pts in this group are older at symptoms onset (mean age 42 yrs) and with reduced diagnostic delay compared to “post-infective” etiology (13 yrs).</td>
</tr>
<tr>
<td>Post-infective</td>
<td>Pts reporting a history of symptoms onset within 10 yrs of a severe respiratory tract infection, such as pneumonia, whooping cough or complicated measles infection. It includes post-tuberculous BE. Pts in this group are younger at symptoms onset (mean age 19 yrs) but with prolonged diagnostic delays (26 yrs). They are more likely to have a history of childhood infections, including pneumonia. They are also more likely to have a history of rhinitis and lobectomy.</td>
</tr>
<tr>
<td>King et al. 2009[9]</td>
<td>Mostly women with longer duration of productive cough; higher prevalence of rhinosinusitis, exacerbations per year (mean 3/yr) and presence of crepitations on physical exam. Worse PFTs and radiological alterations. Higher proportion of adequate sputum specimens for microbiological analysis and higher incidence of P. aeruginosa.</td>
</tr>
</tbody>
</table>

BE: Bronchiectasis, pts: Patients, yrs: years, COPD: Chronic obstructive pulmonary disease.

Table 2: Bronchiectasis Severity Scores

<table>
<thead>
<tr>
<th>Bronchiectasis Severity Index (17)</th>
<th>FACED score (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1% predicted</td>
<td></td>
</tr>
<tr>
<td>&gt; 80</td>
<td>0 points</td>
</tr>
<tr>
<td>50-80</td>
<td>1 point</td>
</tr>
<tr>
<td>30-49</td>
<td>2 points</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>3 points</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>0 points</td>
</tr>
<tr>
<td>50-69 years</td>
<td>2 points</td>
</tr>
<tr>
<td>70-79 years</td>
<td>4 points</td>
</tr>
<tr>
<td>≥ 80 years</td>
<td>6 points</td>
</tr>
<tr>
<td>Chronic bacterial colonization</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>3 points</td>
</tr>
<tr>
<td>other organisms</td>
<td>1 point</td>
</tr>
<tr>
<td>None</td>
<td>0 points</td>
</tr>
<tr>
<td>Number of lobes with BE</td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>0 points</td>
</tr>
<tr>
<td>&gt; 2 or cystic BE</td>
<td>1 point</td>
</tr>
<tr>
<td>Dyspnea, mMRC score</td>
<td></td>
</tr>
<tr>
<td>≤ 3</td>
<td>0 points</td>
</tr>
<tr>
<td>4</td>
<td>2 points</td>
</tr>
<tr>
<td>5</td>
<td>3 points</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>2 points</td>
</tr>
<tr>
<td>≥ 18.5</td>
<td>0 points</td>
</tr>
<tr>
<td>Hospital admissions in the past 2 years</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 points</td>
</tr>
<tr>
<td>No</td>
<td>0 points</td>
</tr>
<tr>
<td>Exacerbation frequency in the past 12 months</td>
<td></td>
</tr>
<tr>
<td>&lt; 3</td>
<td>0 points</td>
</tr>
<tr>
<td>≥ 3</td>
<td>2 points</td>
</tr>
</tbody>
</table>

BSI: 0-4 points, low risk of hospitalization and mortality, 5-8 points: moderate risk of hospitalization and mortality, ≥9 points: high risk of hospitalization and mortality. FACED score: low risk 5-year all-cause mortality (0-2 points), moderate risk of mortality (3-4 points), high risk of mortality (5-7 points). FEV1: Forced expiratory volume in the 1st second, BE: Bronchiectasis, mMRC scale: Modified Medical Research Council Scale, BSI: Bronchiectasis Severity. yrs: years, COPD: Chronic obstructive pulmonary disease.

presence of dyspnea (evaluated through the modified Medical Research Council Scale [mMRC]). These scoring systems were created to predict patients at high risk of mortality, hospitalization, and exacerbations in the case of the BSI, or only mortality in the case of the FACED score. Recently, Li et al. from China created and validated a scoring system for identifying patients at risk of exacerbations.[19] Most of the proposed items were similar to those by Chalmers et al. and Martínez-García et al., including age, dyspnea evaluated through the mMRC scale, *Pseudomonas aeruginosa* colonization, extension of radiological involvement, and PFTs impairment. The authors also included the presence of prior intensive care unit admission.
Several studies compared the BSI and the FACED scores. Ellis et al. found that both scoring systems had similar predictive power for 5-year mortality, with the FACED score showing slightly superior predictive power for 15-year mortality. The BSI was also developed to predict the risk of hospitalization and exacerbations. A recently published study by McDonnell et al. directly compared BSI and FACED scores for the assessment of clinically relevant disease outcomes across seven European cohorts. The study showed that both scores accurately predicted mortality, but BSI was superior to FACED in predicting multiple outcomes, including hospital admissions, exacerbations, quality of life, and lung function decline. The ability of predicting not only mortality but also other clinically relevant outcomes supports the utility of BSI in “real-life” decision-making processes. Patients at high risk may benefit from aggressive treatment while those at low-risk could receive nonspecialist follow-up or simpler treatment regimens. Data to validate this approach are now needed.

While severity scores provide an important piece of the puzzle formed by the patient and their disease, they do not allow a personalized approach, with, for instance, two very different clinical cases characterized by similar BSI or FACED scores and different clinical management [Table 3].

**PHENOTYPING ACCORDING TO CLINICAL AND MICROBIOLOGICAL CHARACTERISTICS WITH A CLUSTER-BASED APPROACH**

The third approach that has emerged more recently is cluster-based analysis.

Cluster analysis refers to a group of multivariate mathematical algorithms that broadly perform two distinct functions: (1) quantification of similarity between individuals within a population on the basis of (multiple) specified variables; (2) grouping of individuals into clusters such that similarity between members of the same clusters is strong, while similarities between members in different clusters is weak. Furthermore, to validate the primary cluster analysis, independent external cohorts are recruited.

In recent years, several phenotypes for asthma and COPD have been proposed. Two kinds of phenotypes of asthmatic patients have been used: clinical (e.g., allergic, aspirin-sensitive, and glucocorticoid-resistant asthma) and pathophysiological phenotypes (e.g., eosinophilic, neutrophilic, mixed inflammatory, and paucigranulocytic asthma). These approaches are sometime referred to (clinical) phenotyping and endotyping, respectively.

The former category is helpful to clinicians because it can be detected through clinical history and physical examination. The latter category is important for pharmacologists, allowing the development of therapies targeted to the pathophysiological mechanisms of the disease. The distinction between phenotypes allows the clinician to identify the best-individualized treatment.

Focusing on BE, to date, there are three main studies describing clinical phenotyping.

Aliberti et al. performed a principal component and cluster analyses using data from five European BE registries (1145 patients). The authors identified four clinical phenotypes mainly based on microbiological isolations and respiratory symptoms [Table 4]. These groups differ from one another both from a therapeutic and prognostic point of view. In the Pseudomonas cluster, more than 50% of the patients were exposed to a macrolide, and more than one-third were on inhaled antibiotic treatment; this cluster also showed higher rates of exacerbations, hospitalizations, and mortality rate during the 3-year follow-up period. One-third of the patients in the “other chronic infection” and “daily sputum” clusters were on long-term macrolides, while few patients received inhaled antibiotic therapy; these two clusters also shared a similar 3-year mortality rate and number of hospitalizations at 1-year follow-up. The “dry BE” cluster showed the best outcomes and rarely received antibiotic maintenance therapy.

Guan et al. performed a hierarchical cluster analysis on a data set of 148 adult Chinese patients with BE. Clusters were defined by patient’s age at symptoms’ onset and past clinical history [Table 4]. Cluster #2 and, secondly, Cluster #3, showed similarities with the Pseudomonas group of the study by Aliberti et al. These two clusters showed more extensive radiological and functional involvement, which translated into a greater severity of disease with more respiratory symptoms and worse quality of life. P. aeruginosa colonization was common in both groups. Furthermore, similarly to the Pseudomonas cluster, these two groups showed high rates of macrolide therapy, increased number of BE exacerbations in the previous 2 years and increased health-care utilization. Guan et al. also described cluster #1, which showed mild disease severity and shared some characteristics with the “dry BE” group by Aliberti et al. The main feature of this cluster was the reduced health-care utilization.

Martinez-García et al. in a recently published multicenter study described the results of a cluster analysis involving 468 patients from six Spanish BE reference centers. The most severe cluster of patients described in this cohort is the “elderly/severe/exacerbators” phenotype. This group shared many characteristics with the Pseudomonas and “daily sputum” phenotypes by Aliberti et al. and Clusters 2–3 in the study by Guan et al. In fact, patients in this group were the oldest, the most symptomatic not only for breathlessness but also for purulent sputum production, the most likely to have an active
or prior smoking habit and to have COPD as comorbidity. Furthermore, this cluster showed a high prevalence of *P. aeruginosa* and *Haemophilus influenzae* colonization. Chronic treatment with macrolides and inhaled antibiotics were used in 34% and 46% of cases, respectively. This group showed the worst outcomes, including a high number of exacerbations in the prior year and an increased mortality for respiratory causes. Martínez-García *et al.* also described a phenotype defined as “elderly/severe/non-exacerbators” that, differently from all the phenotypes described in the other studies, was characterized by a high mortality rate, but mainly due to non-respiratory causes (cardiovascular diseases and neoplasms). Interestingly, these patients showed relatively low chronic colonization with *H. influenzae* and *P. aeruginosa*, low number of exacerbations in the prior year, and low use of chronic macrolides and inhaled antibiotics. Probably, the poor outcomes in this cluster were mainly associated with comorbidities and not with BE itself.

The phenotypes presented so far are very useful from a clinical point of view; however, their usefulness in understanding the biological mechanisms and pathophysiology of the disease is less clear and further studies are required.

As observed by the previously described studies, some phenotypes may present similar characteristics. This is the case for patients in the BE-COPD overlap syndrome group by Buscot *et al.*, the *Pseudomonas* and “daily sputum” phenotypes by Aliberti *et al.*, Cluster #3 by Guan *et al.*, and the “elderly/severe/exacerbators” phenotype by Martínez-García *et al.*[^7] In particular, BE patients with COPD are usually elderly, very symptomatic subjects with multiple comorbidities, and severe functional impairment.

The differences and similarities between the proposed phenotypes reflect the heterogeneity of patients worldwide and the need to individualize clustering at local and national level.

### ENDOTYPING OF BRONCHIECTASIS

In the era of targeted therapies in asthma, certain endotypes have emerged, including high and low eosinophils and periostin groups.[^26,27] The characterization of BE endotypes could include the evaluation of cellular and soluble factors. A recent study by Dente *et al.* showed higher levels of neutrophil bronchial inflammation in BE patients with bacterial colonization, especially with *P. aeruginosa* and elevated BSI.[^23] Higher levels of free neutrophil elastase activity, myeloperoxidase activity, and interleukin (IL)-1β were also found by Aliberti *et al.* in the “*Pseudomonas*” and “other chronic infection” clusters, confirming the high levels of neutrophil inflammatory markers in patients with bacterial colonization.[^4]

Some soluble inflammatory markers and, particularly a deregulated cytokine network, including IL-8, tumor necrosis factor-alpha, and neutrophil elastase are also plausible candidates in BE pathogenesis and, thus, potentially useful in endotyping.[^29]
Younger patients (mean age 40 yrs) with shorter time since symptoms onset, with predominantly mild disease from young women with low BMI, mild disease and no frequent exacerbators. Absence of airflow obstruction. Presence of respiratory symptoms (mainly chronic cough, hemoptysis, and dyspnea) and extensive radiological impairment. More severe functional alterations involving PFTs and performance status, with increased need for LTOT and worse quality of life. Increased activation of the inflammatory system during stable state. All these factors lead to a higher severity and to a more rapid progression of the disease, which ultimately translates into an increased number of exacerbations and hospitalizations and a higher 3-year mortality. Pts in this group show more often a post-infectious etiology.

Elderly pts with shorter duration of symptoms and mostly idiopathic BE. This cluster presents the most severe form of BE both radiologically and functionally. Most pts have P. aeruginosa colonization (59%), and frequent health care resource use. This cluster comprises the highest number of pts with cystic BE (96%) and atelectasis (55%). 6-minute walk distance is the lowest among all clusters, accompanied by low quality of life.

Elderly overweight women with mild disease and no frequent exacerbators. Presence of mild airflow obstruction. Main BE etiologies: idiopathic, post-infectious or asthma. Low rate of non-respiratory comorbidities and chronic bronchial infections.

Elderly pts with modest time since symptoms onset and moderate disease severity. A few patients have P. aeruginosa colonization (17%). This group shows modest use of healthcare resources without quality of life impairment.

Young women with low BMI, mild disease and no frequent exacerbators. Absence of airflow obstruction. Main BE etiologies are: genetic/immune deficiency, post-infectious or idiopathic. Low rate of non-respiratory comorbidities and chronic bronchial infections.

Elderly overweight women with mild disease and no frequent exacerbators. Presence of mild airflow obstruction. Main BE etiologies: idiopathic, post-infectious or asthma. Low rate of non-respiratory comorbidities and chronic bronchial infections.

Elderly men with moderate-severe disease, high prevalence of chronic bronchial infection, severe flow obstruction, and frequent exacerbations. Main BE etiologies: post-infectious and COPD-associated. Low rate of non-respiratory comorbidities.

Elderly pts with moderate-severe disease, severe flow obstruction, low number of exacerbations and moderate chronic bronchial infection rate. Main etiologies: post-infectious and idiopathic. High rate of non-respiratory comorbidities (cardiovascular and neoplasms).

These findings suggest that further multicenter studies on BE phenotyping-endotyping are required to better understand both the pathogenesis of the disease and possible therapeutic targets.

This approach has already lead to new therapeutic advances in asthma. In BE patients, Wells et al. have recently demonstrated “blocking antibodies” that protect P. aeruginosa from complement-mediated killing in a very severe subpopulation with P. aeruginosa infection. This abnormality of humoral response appears to be characterized by excess production of O-antigen-specific IgG2 antibodies and patients with this “endotype” have more marked disease severity. This form of endotyping may allow us to tailor-specific treatments beyond that suggested by the clinical phenotyping alone.

THERAPEUTIC IMPLICATIONS AND CLINICAL MANAGEMENT

BE patients grouping on the basis of clinical, microbiological, and etiological criteria have implications for the prognosis and the therapeutic management of the disease. Patients may require individualized treatments based on clinical phenotypes.

On the one hand, phenotypes such as “dry BE” in the study by Aliberti et al. and patients not colonized by pathogenic bacteria, with few respiratory symptoms and low severity of
the disease, do not usually require a close follow-up. Those patients after an initial assessment with general therapeutic indications (e.g., airway clearance techniques, prevention of exacerbations/respiratory infections, and bronchodilation if indicated) may be followed up by the general practitioner. Some data suggest that up to 30% of these patients may acquire P. aeruginosa, so ongoing microbiological surveillance, albeit at a low frequency, may be helpful.\[52]\]

On the other hand, patients with chronic infections, particularly those with P. aeruginosa, require closer follow-up; in those cases, monitoring of sputum cultures, both during exacerbations and stable state, becomes of primary importance. These patients are candidates for targeted therapy, using inhalational antibiotics, for bacterial eradication or reduction of bacterial load.

Recently, a single-center retrospective study on the real-life use of nebulized antibiotics aimed to characterize the clinical phenotype of patients that most benefit from such treatment.\[33]\] BE patients with a greater number of exacerbations, a lower lung function, a greater presence of nodules and cysts on computed tomography scan, and higher BSI score seemed to represent a sort of “higher risk” cluster of patients that showed the best outcomes after aerosolized antibiotics.

Other particular BE phenotypes may require specific therapeutic approaches. As an example, COPD-associated BE may require counseling for smoking cessation and personalized rehabilitation programs. Such patients may also be the ones, in whom targeted screening for alpha-1 antitrypsin deficiency provides a better yield than other etiologies.

**FUTURE PROSPECTIVES**

Although much progress has been achieved recently in characterizing BE both from a prognostic and clinical point of view, many advances are still needed in the therapeutic field. A better knowledge of the BE etiology, with specific reference to treatable causes,\[33]\] the increasingly widespread use of long-term macrolide therapy,\[14-30]\] as well as a greater attention to the prevention of BE exacerbations, and to the role of the respiratory therapists have definitely improved clinical practice. However, the issue of airways bacterial colonization, which seems to be one of the most important factors in the severity of the disease, should be adequately addressed, particularly in terms of pulmonary targeted antimicrobial therapy. Both nebulized and dry powder inhaled antibiotics are available for use in cystic fibrosis.\[37]\] To date, the available studies mainly focused on P. aeruginosa chronic infection, reported worse outcomes, with bacterial eradication only in a few cases.\[38-40]\] Furthermore, nebulized antibiotics may be associated with side effects (e.g., five times increase in bronchospasm reported with inhaled aminoglycosides compared to placebo).\[41]\] Therefore, better selection of the candidates for inhaled antibiotics, as previously described, as well as new molecules or better formulations of the available ones could improve patients’ outcomes.

Finally, in regard to phenotyping, future studies should aim to assess the applicability in clinical practice of the previously described clusters and their power to predict differential responses to therapy, to inform on the design of future randomized control trials.

**CONCLUSIONS**

The need of personalizing the management of BE patients has been internationally recognized as a research priority in the field.\[42]\] The elements that seem to better define the severity of BE phenotypes are the presence of chronic bronchial infections, primarily with P. aeruginosa, secondly, with other bacteria, and the presence of chronic respiratory symptoms. The evaluation of the etiology of BE suffers from several limitations, and the need of collecting data at a multi-country level seems to play a secondary role, with the only exception of COPD-associated BE.\[43]\]

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**Conflicts of interest**

There are no conflicts of interest.

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