Minireview

The clinical phenotype of bronchiectasis and its clinical guiding implications

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Impact statement

Bronchiectasis is a chronic respiratory disease with great heterogeneity in terms of clinical presentation, and it is of great importance to explore its phenotype for individualized treatment. This review summarizes the current research progress in phenotypic classification of bronchiectasis, cluster analysis methods for identifying new phenotypes from a statistical perspective, and tools for evaluating disease severity. The purpose of this review was to provide meaningful suggestions for clinical treatment and management.

Abstract

Bronchiectasis is a chronic airway disease with abnormal and persistent bronchial dilatation caused by a variety of reasons. In recent years, numerous reports have shown that bronchiectasis is heterogeneous, the clinical characteristics of patients with different phenotypes are different, and the efficacy of a treatment regimen may vary greatly in patients with different bronchiectasis phenotypes. This paper summarizes the current clinical phenotypic classification of bronchiectasis from the perspective of etiology, microbiology, and the frequency of acute exacerbation, and cluster analysis was used to determine new clinical phenotypes and their statistical and clinical significance. Different tools for assessing disease severity yield different outcomes. This article summarizes the research progress in the above areas, hoping to provide a more comprehensive understanding of the disease.

Keywords: Bronchiectasis, phenotype, etiology, microbiology, deterioration frequency, cluster analysis

***Experimental Biology and Medicine* 2021; 246: 275–280. DOI: 10.1177/1535370220972324**

Introduction

Bronchiectasis refers to the irreversible dilation of one or more of the proximal bronchi with a diameter larger than 2 mm due to the destroyed bronchial wall muscles and elastic supporting tissues which are caused by infection, physicochemical, immune or genetic reasons, and it is deemed to be the most usual outcome of airway injury. The main clinical manifestations are chronic cough, sputum production, and/or repeated hemoptysis, which seriously affect lung function and ultimately lead to a lower quality of life. In 2013, the prevalence of bronchiectasis in American adults was 0.139%.[1] Due to the lack of attention to bronchiectasis in China, there are no epidemiological data on the disease. It is estimated that the overall prevalence of bronchiectasis diagnosed by physician is 1.2% in population aged $\geq$40 years. Moreover, the prevalence rate is on the rise with the aging of the population.[2] Because the number of undiagnosed individuals is unknown, the actual prevalence rate is more than 1.2%,[3] bringing about an increasingly serious economic and health burden. High-resolution computed tomography (HRCT) is the main method used to diagnosis bronchiectasis.[4]

The heterogeneity of bronchiectasis is manifested by multiple etiologies, related to infection, idiopathy, chronic obstructive pulmonary disease (COPD), asthma, congenital conditions, immunodeficiency, autoimmune diseases, and tumors, and has a broad range of clinical features, ranging from focal lesions in one lobe to diffuse lesions in both lungs involving all lobes, from subtle airway expansion to cystic changes.

Clinical phenotype

Phenotype refers to the observable characteristics of an organism and is the result of the interaction of genetic and environmental factors and the basis for classifying organisms. Different studies have attempted to classify bronchiectatic patients according to etiology (Table 1), microbiology, and frequency of acute exacerbation to achieve precise treatment and improve prognosis.

Etiology

Buscot *et al.*[5] classified 311 bronchiectasis patients into the following three main groups from the perspective of

Table 1. Clinical phenotypes classified by etiology.

References	Nation	Number of cases	Characteristics of clinical phenotypes
Buscot *et al*.[5]	France	311	Postinfectious bronchiectasis (50%), non-postinfectious bronchiectasis (39%), and idiopathic bronchiectasis (11%)
Anwar *et al*.[6]	United Kingdom	189	Postinfectious bronchiectasis (24%), non-postinfectious bronchiectasis (33%), and idiopathic bronchiectasis (43%)
Guan *et al*.[7]	China	148	Idiopathic (46.0%), postinfectious (27.0%), and immunodeficiency (8.8%)

etiology: postinfectious bronchiectasis (PIB, 50%), non-postinfectious bronchiectasis (39%), and idiopathic bronchiectasis (IB, 11%). Postinfectious bronchiectasis was mostly related to tuberculosis (55%). The others involved whooping cough (15%), unspecified pathogen (12.5%), measles (7.5%), Swyer-James syndrome (5%), legionella (2.5%), and non-tuberculous mycobacteria (2.5%). Among non-postinfectious bronchiectasis patients, COPD was the most common cause (33%), followed by congenital bronchiectasis (17%). COPD-related bronchiectasis mainly occurred in men (male/female ratio = 2.22) and was obviously associated with smoking. The patients in this study were the oldest and had the lowest FEV_1 (forced expiratory volume in one second) at diagnosis, with a high detection rate of *Pseudomonas aeruginosa* in their sputum (65%). Congenital bronchiectasic patients were the youngest when diagnosed with the lowest smoking rate (13%); 93% of patients had latent microorganisms in their sputum, and 57% of the cases had *P. aeruginosa*. The majority of patients with idiopathic bronchiectasis were women (male/female ratio= 0.23), and only 15% of them had a smoking history. In this group, patients had the best FEV_1 at diagnosis with a lower infection rate of *P. aeruginosa* (30%) than patients with the other types of bronchiectasis. The study identified three specific phenotypes of bronchiectasis among all etiologies: idiopathic, congenital, and COPD-related. Because of the high prevalence and incidence of *P. aeruginosa*, especially in patients with COPD, it is meaningful to eradicate this pathogen and improve treatment for those with it.

Anwar *et al*.[6] investigated 189 British patients with bronchiectasis, and the congenital etiology accounted for 57% of the cases. There were three main phenotypes: postinfectious bronchiectasis (24%), non-postinfectious bronchiectasis (33%), and idiopathic bronchiectasis (43%). The onset age of patients with PIB was significantly younger compared with that in patients with IB and *Pseudomonas* infection in sputum. Anwar *et al.* considered that patients with allergic bronchopulmonary aspergillosis and total immunoglobulin deficiency should receive special treatment. In addition, routine screening for other causes was not considered necessary.

These are the characteristics of Western populations. The etiologies of bronchiectasis in mainland China are not clear compared with those in Western countries. Guan *et al*.[7] investigated 148 patients with stable bronchiectasis in Guangzhou, South China. This was the first study to record the etiologies of bronchiectasis in mainland China. Idiopathic bronchiectasis (46%), postinfectious bronchiectasis (27%), and immunodeficiency (8.8%) were the most common causes. Among the known causes, measles (9.5%) and tuberculosis (10.8%) were the most commonest causes in the postinfectious group, accompanied by immunodeficiency (8.8%) and asthma (5.4%). Other known causes account for 8.8%. There was no significant difference in clinical characteristics between patients with idiopathic bronchiectasis and patients with known etiologies. The study concluded that the etiological profile of bronchiectasis showed no obvious geographic or ethnic differences.

Bronchiectasis combined with COPD has been recognized as a serious clinical phenotype of COPD. Several investigations showed that 4%–72% of patients with moderate to severe COPD were complicated with bronchiectasis.[8,9] This broad range came from several groups, there were different study objectives, inclusion criteria, study population, and even methodologies used in their studies.[10–16] These differences may interpret the discrepancy observed in the reported prevalence. The COPD bronchiectasis phenotype has special clinical characteristics, such as an excessive sputum volume, a higher risk of bacterial infection, including infection with *P. aeruginosa*, higher systemic and local inflammatory indexes, more frequent acute exacerbations, poor nutritional status, more severe airflow restriction, and immune imbalance.[17,18] These patients need to be treated for the two situations simultaneously as recommended in the corresponding guidelines. Some scholars have proposed that the area under the forced expiratory flow-volume loop is more suitable for the evaluation of emphysema in patients with bronchiectasis and COPD than the traditional parameters of spirometry and chest CT for guiding follow-up treatment.[19]

At present, the treatment of bronchiectasis mainly focuses on the clearance of sputum and rational application of antibiotics. A systematic etiological examination can reduce the proportion of idiopathic bronchiectasis cases and further ameliorate the management of patients with special etiologies such as allergic bronchopulmonary aspergillosis.

Microbiology

A meta-analysis found that *P. aeruginosa*, one of the most common pathogens which always were isolated from the sputum of bronchiectasic patients, had adverse effects on inflammation, lung function, admission, acute exacerbation, mortality, and quality of life in bronchiectasic patients.[20] Martinez-Garcia *et al*.[21] also confirmed that the lung function of patients with *P. aeruginosa* infection decreased faster than that of those infected with other organisms. Menéndez *et al.* found that continuously

increasing systemic inflammation appeared in bronchiectasic patients after the acute phase. Patients infected with *P. aeruginosa* at exacerbation were observed as having the highest levels and persistence of IL-17a.[21] Similar results were reported in *P. aeruginosa*-infected rats with bronchiectasis.[22] It is well documented that IL-17a is secreted by Th17 cells to participate in the inflammatory process of bronchiectasis, showing that Th17/Treg imbalance may be an important mechanism for bronchiectasis. Therefore, IL-17a could be a target treatment for modulating the inflammatory process of bronchiectasis. In addition, Fouka *et al.*[23] reported that there were reduced response of both systemic and local Th17 in patients with non-CF bronchiectasis treated with prophylactic, low-dose clarithromycin administration, suggesting a potential anti-inflammatory and/or immunomodulatory effect of clarithromycin on non-CF bronchiectasis. At present, the national guidelines on bronchiectasis recommend that the remedy for eradication of *P. aeruginosa* is mainly for cases of bronchiectasis caused by cystic fibrosis. This study provided medical evidence for the eradication of *P. aeruginosa* in bronchiectasis caused by noncystic fibrosis. Moreover, studies have shown that a large proportion of patients can eradicate *P. aeruginosa*, and eradication of *P. aeruginosa* can reduce the frequency of acute exacerbation, improving the respiratory symptoms and prognosis of patients.[24] Inhaled antibiotics have been recommended for the treatment of bronchiectasis in recent years due to their advantages, such as a high local blood concentration, little effect on liver and kidney function, few adverse reactions, and convenience of administration. It was found that although the eradication of *P. aeruginosa* by inhaled antibiotics could not significantly improve the pulmonary function and quality of life of patients, it could extend the time until the first acute exacerbation and reduce the frequency of acute exacerbations and the bacterial load in sputum, and it was well tolerated.[25] Individuals vulnerable to *P. aeruginosa* infection could benefit from a *P. aeruginosa* vaccine. The experiment had demonstrated that *P. aeruginosa* vaccine is protective in a chronic lung infection animal model, significantly reducing the number of bacteria recovered 4 h after acute challenge with *P. aeruginosa*.[26] In this model, there was much less epithelial thickening in the bronchiole wall, less cellular infiltration, less alveolar wall damage, and less lung consolidation in immunized animals compared with non-immunized controls.[27] Despite some animal experiments and preliminary clinical studies, there is no licensed vaccine for *P. aeruginosa*. Some scholars have investigated the related risk factors for *P. aeruginosa* infection in patients with bronchiectasis. Related factors of PA-resistant isolates in bronchiectasis included the use of antibiotics previously, repeatedly exacerbations in recent year, greater radiologic severity, and higher scores of modified Medical Research Council dyspnea.[28] In view of the significant impact of *P. aeruginosa* on all aspects of patients, screening for its risk factors is particularly important. As an important risk factor for the prognosis and severity of the disease, *P. aeruginosa* infection has been included in various scoring systems to assess the severity of bronchiectasis, such as the FACED/E-FACED score and the bronchiectasis severity index (BSI). The difference in the prevalence rate of *P. aeruginosa* at home (30%) vs. abroad (10%–30%) may be related to the widespread use of antibiotics in China, the increasing prevalence of multidrug-resistant *P. aeruginosa*, ethnicity, meteorology, and the severity of bronchiectasis.[7]

The mechanism of action of nontuberculous mycobacteria (NTM), fungi and viruses in bronchiectasis has rarely been studied. Schweitzer *et al*.[29] found that the mycobacterium avium complex was the most common bacteria among NTM. Older women and those with low weight are more susceptible to NTM. The findings of McDonnell *et al*.[30] are consistent with those of Schweitzer. Bronchiectasis caused by NTM is most likely to occur in the right middle bronchus. Foreign studies have found that patients with bronchiectasis who are infected by NTM may have a special immune phenotype characterized by an imbalance of adipokines and related cytokines; the specific mechanism needs to be further explored.[31] Fungal colonies isolated from the respiratory tract of bronchiectasic patients were mostly Candida and Aspergillus.[32] Several results showed that the most common viruses detected in bronchiectasic patients were coronaviruses, rhinoviruses, and influenza viruses. The detection rate of viruses in patients with acute exacerbation was higher than that in patients in a stable stage, also the detection rate of viruses in patients with moderate to severe bronchiectasis was higher than that in patients with mild bronchiectasis.[33,34] This indicates that viruses are involved in acute exacerbation of bronchiectasis, but the mechanism of action is elusive. The inflammation in patients with mixed viral and bacterial infections is more severe than that in patients with infection by a single virus,[33,34] so we need to pay attention to dual infections in patients with an acute exacerbation.

Due to the differences in the clinical characteristics of susceptible populations and patients being caused by different microorganisms, it is very important to detect the categories of microorganisms to develop and apply reasonable targeted antibiotic therapy. In addition, targeted therapy (e.g. IL-17a) and *P. aeruginosa* vaccine are promising therapeutic strategies for patients with bronchiectasis. We should make these treatments more mature. Continue to carry out research on *P. aeruginosa* vaccine and obtain a vaccine that can be used by human. If possible, not only preventive vaccines, but also therapeutic vaccines.

Frequency of acute exacerbation

Chalmers *et al*.[35] reported that patients with frequent acute exacerbations, especially those with more than two times of exacerbations per year at baseline, had poorer quality of life, a higher hospitalization frequency, and increased mortality within five years. So, a past history of exacerbations was the most powerful predictor of future exacerbations. Additionally, independent predictors of the frequency of future exacerbations also included the infection of *P. aeruginosa* and *Haemophilus inuenzae*, radiological severity of disease, FEV1, as well as coexisting COPD.

In clinical practice, appropriate preventive measures, such as prophylactic use of antibiotics and pulmonary rehabilitation, should be taken to reduce the frequency of acute exacerbation in patients with this phenotype.

Application of cluster analysis in phenotypic classification of bronchiectasis

Cluster analysis is a simple statistical method that classifies research objects according to their inherent laws and can be used for phenotypic analysis. Some scholars have used cluster analysis to identify new phenotypes of bronchiectasis (Table 2). Martinez-Garcia *et al*.[36] classified 468 patients with bronchiectasis into four meaningful clinical phenotypes by using cluster analysis as follows: Phenotype 1 (young/moderate): young women without overweight had mild disease, mild idiopathic bronchiectasis, mild genetic, or immune deficiency etiologies. Phenotype 2 (elderly/mild): elderly women with overweight who had mild disease, mild idiopathic, or postinfectious etiologies. Phenotype 3 (elderly/severe/exacerbator): elderly men who had severe disease, a high prevalence of *P.aeruginosa* infection, postinfectious bronchiectasis, multiple exacerbations, severe flow obstruction, and associated COPD. Phenotype 4 (elderly/severe/nonexacerbator): elderly patients who had severe disease but a low number of exacerbations. They discussed the prognostic implications of these clinical phenotypes. Phenotypes 1 and 2 showed similarly low mortality (3.9% and 7.6%, respectively); however, phenotypes 3 and 4 displayed analogously high mortality (37% and 40.9%, respectively). The mortality rate is higher in phenotype 2 was significantly higher than that in phenotype 4 (77.8% vs. 34.4%) due to respiratory causes. Alibert *et al*.[37] identified four clusters according to the presence of chronic infection with *P. aeruginosa* or other pathogens and daily sputum, in 1145 patients with bronchiectasis: "Pseudomonas" (16%), "Other chronic infection" (24%), "Daily sputum" (33%), and "Dry bronchiectasis" (27%). Compared with all the other clusters, the patients infected by *Pseudomonas* exhibited the most severe disease along with the highest inflammatory patterns and worst radiological, the lowest lung function, the greatest number of exacerbations and hospitalizations, and the worst quality of life at baseline. Patients with dry bronchiectasis were the least severe, with those with other chronic infections and daily sputum having moderate severity. This finding highlights the importance of sputum monitoring in patients with bronchiectasis and provides evidence for the safety and effectiveness of treatment for the eradication or long-term inhibition of *P. aeruginosa*.

Guan *et al*.[38] analyzed 148 adults with stable bronchiectasis. Cluster 1 contained the youngest patients who had predominantly mild and idiopathic bronchiectasis. Cluster 2 consisted predominantly of patients with postinfectious bronchiectasis. Compared to cluster 1, the patients in cluster 2 had longer symptoms duration, greater disease severity, poorer lung function, and airway *P. aeruginosa* colonization (59.1%). Cluster 3 comprised elderly patients who had a shorter symptoms duration, mostly idiopathic bronchiectasis and predominantly severe bronchiectasis. Cluster 4 contained mostly elderly patients who had moderate disease severity. The study showed that patients in clusters 2 and 3 tended to have a greater risk of bronchiectasis exacerbations than those in clusters 1 and 4. Therefore, in-depth follow-up is needed to change the future treatment mode, standardize and guide daily medication use, reduce acute exacerbations, improve respiratory symptoms and quality of life, reduce medical-related expenditures and the waste of medical public resources, and provide timely guidance for medical treatment once the symptoms of acute exacerbations occur.

Cluster analysis avoids the influence of subjective factors of classification. By analyzing patients with similar clinical characteristics or prognoses, clinical phenotypes can be identified, contributing to targeted treatments and interventions in future randomized controlled trials that could change the natural course of the disease.

Advances in tools for assessing the severity of bronchiectasis

The severity or prognosis of bronchiectasis cannot be precisely defined using a single variable since it is a multifaceted disease. Nearest published multidimensional scores combine clinical features, pulmonary function,

Table 2. Cluster analysis of bronchiectasis cases.

References	Number of cases	Cluster characteristics
Martinez-Garcia *et al*.[36]	468	Phenotype 1: young/moderate/genetic and/or immune deficiency/idiopathic Phenotype 2: elderly/mild/idiopathic/postinfectious Phenotype 3: elderly/severe/exacerbator/high prevalence of *Pseudomonas aeruginosa* infection/postinfectious and associated COPD Phenotype 4: elderly/severe/nonexacerbator
Aliberti *et al*.[37]	1145	Cluster 1: *Pseudomonas* (16%) Cluster 2: Other chronic infection (24%) Cluster 3: Daily sputum (33%) Cluster 4: Dry bronchiectasis" (27%)
Guan *et al*.[38]	148	Cluster 1: youngest/mild/idiopathic Cluster 2: postinfectious/longest duration of symptoms/greater disease severity/poorer lung function/airway *Pseudomonas aeruginosa* colonization (59.1%) Cluster 3: elderly/shorter duration of symptoms/idiopathic bronchiectasis/severe Cluster 4: most elderly/moderate

Table 3. Differences among different evaluation tools.

Item	BSI	FACED	E-FACED
Age	√	√	√
BMI	√	×	×
FEV_1%predicted	√	√	√
Hospital admission in the past 2 years	√	×	×
Number of exacerbations in previous year	√	×	√
MRC dyspnea score	√	√	√
Pseudomonas colonization	√	√	√
Radiological extension	√	√	√

microbiological and imaging variables to better assess the severity and prognosis of bronchiectasis. Three multidimensional scores are introduced below. Chalmers *et al*.[39] introduced the bronchiectasis severity index (BSI), which includes age, BMI, FEV_1% predicted, hospital admission in the past two years, the number of exacerbations, the MRC dyspnea score, *Pseudomonas* colonization, colonization with other organisms, and radiological severity assessed by a modified Reiff score. Martinez-Garcia *et al*.[40] developed the FACED score. It was constructed with five dichotomized variables: FEV_1% predicted (F); age (A); presence of chronic colonization by *P. aeruginosa* (C); radiological extension (E), and dyspnea (D). The BSI is more complex than the FACED score, but it predicts future hospitalization and acute exacerbation risk in addition to mortality. The E-FACED score was the FACED score plus one additional variable: E (exacerbations); it significantly improved the ability to predict future exacerbations per year while maintaining the simplicity of the FACED score,[41] especially for patients with frequent exacerbations. The differences among the three scoring tools are shown in Table 3. Martinez-Garcia *et al*.[42] also proposed the concept of a "control panel", including three dimensions: clinical severity, biological activity, and impact. The severity reflected the disease's functional impact and its effect on target organs. It consisted of FEV_1, the HRCT score, etiology, and existing comorbidities. The Charlson index and Bronchiectasis Aetiology and Comorbidity Index (BACI) can be used to evaluate the impact of comorbidities. The activity included the purulence of the sputum, the presence of pathogenic microorganisms in respiratory samples, BMI, and the number and severity of exacerbations. The impact reflected the patient's understanding of the severity and activity of the disease by using symptoms and some questionnaires, such as the Quality of Life-B Questionnaire, the mMRC, and the Hospital Anxiety and Depression Scale (HADS) questionnaire. A good scoring tool is conducive to the hierarchical management of patients. Whether the etiology assessment, comorbidities, and quality of life questionnaire should be included in the scoring system in the future is worthy of further study.

Conclusions

Bronchiectasis, as a complex and heterogeneous disease with a high prevalence, should be given increasing attention. Current studies on clinical phenotypes provide evidence-based medicine for individualized treatment. Cluster analysis is a statistical method, and its clinical significance still needs to be found by scholars. Whether there are new clinical phenotypes is one of the key points of future research work. We should focus on multicenter research, improve the epidemiological data to determine the actual prevalence of bronchiectasis in China, summarize the disease characteristics, and design diagnostic and treatment plans that are more in line with populations worldwide.

AUTHORS' CONTRIBUTIONS

GL, QKR, LT, and WHL drafted the manuscript and tables. PM edited, revised, and approved the final version of this manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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