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Asthma and bronchiectasis: Another duo on the respiratory stage

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Abstract:

The overlap between asthma and bronchiectasis (BE) is a challenging topic not only for researchers but also for clinicians. The aim of this review was to explore the latest insight of literature focused on the association between asthma and BE from the epidemiological, clinical, functional, and therapeutical perspectives. The literature search included papers published in English in the PUBMED database in the past 10 years. From a total of 233 findings, after eliminating those nonrelated to the topic and after using additional sources, 32 relevant articles were considered. The main results of the present review highlighted that when the two conditions are associated, patients have poorer clinical outcomes, greater disease severity and exacerbation rates, increased hospitalization trend, and risk for pulmonary complications, compared with each disease alone. As future directions, the need to identify both conditions at an early stage and to offer personalized management of these different phenotypes are goals to be further addressed.

Keywords:

Asthma, bronchiectasis, overlap, personalized management, severe asthma

Introduction

Asthma and bronchiectasis (BE) are two common heterogeneous airway diseases worldwide that can coexist in some patients and therefore raise different clinical, therapeutical, and prognosis implications.[1,2] The association between BE and asthma is an ongoing research topic, which still needs evidence from diverse perspectives.[3] The coexistence of BE and asthma is not rare, but it is often unrecognized and challenging, not only in terms of diagnosis but also regarding

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the impact on different outcomes including therapeutical management and success.[4,5] The fact that both conditions share similarities in terms of clinical manifestations (cough, sputum, wheezing, dyspnea, and obstructive pattern), clinical outcomes, or functional pattern creates even greater challenges in daily clinical practice.[6]

BE may complicate asthma at any age, not only in adults but also in children and adolescents; therefore, complex approaches and management are required.[7]

In our review, we explored the latest insight of literature focused on the overlap between asthma and BE from the epidemiological, clinical, functional, and therapeutical perspectives.

Methodology

This narrative review was based on the search from electronic data sources using the PubMed (MEDLINE) database. There was no need for ethics committee approval as this study was a synthesis of published studies.

The initial search strategy on the keywords bronchiectasis and asthma identified 233 results. When not applied, the Boolean operator AND did not change the total number of results. The publication date of the search was in the past 10 years between January 16, 2011, and October 16, 2021. The search included full-text systematic reviews, reviews, meta-analysis, clinical trials, and randomized controlled trials published in English. We supplemented our electronic database search with additional records relevant to the topic. After eliminating articles nonrelated to the topic, duplicates, and after using additional sources, 32 articles with relevance to the aim of the study were considered. Table 1 provides information about some of the articles considered.

Asthma with comorbid bronchiectasis

Despite recent data focused on the etiopathogenesis of BE, just about 50% of them have a clear cause.[8,9] The perspective that BE is a consequence of asthma and thus needs time to develop is described in numerous studies.[8–10]

In the light of updated evidence, asthma, and in particular long-term uncontrolled asthma, may be seen as a structural and functional airway disorder favoring the development of BE.[3,11] The clear cause and effect relationship between asthma and BE is still debatable[12] and has not yet been precisely established,[3] particularly due to the lack of relevant animal studies.[12] Despite these uncertainties, bronchial asthma is considered the sixth leading cause of BE with a range between 3% and 7%.[8] According to the British Thoracic Society recommendations, asthma needs to be considered as a cause of BE in the absence of other etiologies.[13–15]

With the increased use of the thoracic high-resolution computed tomography (HRCT), the presence of BE in asthmatics, particularly in the severe phenotypes,[16–18] is more frequently identified, with a range from 0.8% to 77% according to real-life data.[9,16,19–21] The role of the HRCT in the diagnosis of BE in different chronic obstructive lung diseases including asthma patients is of greatest value, as for many years, the data about the presence of the bronchial dilatation in asthmatics (25%) were mainly obtained from Dunnill's autopsy findings in 1960,[22] though in the pediatric population with severe asthma, there is poor evidence of routine use of HRCT.[7,23] The destruction of the bronchi and the permanent airway remodeling by an inflammatory process or recurrent infection are possible explanations for the prevalence of bronchial dilation in asthma patients.[24]

Another possible link between the two diseases was related to the immunoglobulin (Ig) and IgG subclass deficiency.[25,26] Toward these data, a recent finding of Luján et al.[27] was that the prevalence of BE in asthma seems to be related to the steroid requirements. According to this case-control cross-sectional study, steroid-dependent asthma seems to be at higher risk for BE, compared with non-steroid-dependent asthma. A possible explanation is a disease itself, not other contributors like the Ig levels.[27]

BE should be considered as both a differential diagnosis for and a comorbidity in asthmatics, particularly in long-standing or severe asthma.[28] A common pitfall in clinical practice is that sometimes in asthmatics the clinical features of BE are less visible due to the symptoms of asthma.[3,10]

In the light of these results, the current international asthma and chronic obstructive pulmonary disease (COPD) guidelines[29,30] recommend investigating the possible coexistence of BE defined as "treatable trait."

Table 1: Most relevant information documents

Author	Year	Title	Article type
Chen FJ, Liao H, Huang XY, Xie CM	2016	Importance of fractional exhaled nitric oxide in diagnosis of bronchiectasis accompanied with bronchial asthma	Original article
Padilla-Galo A, Olveira C, et al.	2018	Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: A study in 398 patients	Original article
Zhang SQ et al.	2021	Clinical features of asthma with comorbid bronchiectasis: A systematic review and meta-analysis	Systematic review and meta-analysis
Crimi C, Ferri S, Campisi R, Crimi N	2019	The link between asthma and bronchiectasis: State of the art	Clinical investigation
Polverino E, Dimakou K, Hurst J, et al.	2018	The overlap between bronchiectasis and chronic airway diseases: State of the art and future directions	Review article
Polverino E, Goeminne PC, et al.	2017	European Respiratory Society guidelines for the management of adult bronchiectasis	Task force reports ERS* Guidelines
Maglione M, Aksamit T, Santamaria F	2019	Paediatric and adult bronchiectasis: Specific management with coexisting asthma, COPD, rheumatological disease and inflammatory bowel disease	Review article
Lonni S et al.	2015	Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity	Original research
Ferri S et al.	2020	Impact of asthma on bronchiectasis severity and risk of exacerbations	Research article
Mäntylä J, Mazur W, Törölä T, et al.	2019	Asthma as aetiology of bronchiectasis in Finland	Research article
Wang D et al.	2016	A morphologic study of the airway structure abnormalities in patients with asthma by high-resolution computed tomography	Original article
Amati F, Franceschi E, Gramegna A, et al.	2017	Investigating the etiology of bronchiectasis: You do not find what you do not look for	Letter to editor
Dimakou K et al.	2018	Investigation of bronchiectasis in severe uncontrolled asthma	Original article
Coman I, Pola-Bibián B, Barranco P, et al.	2018	Bronchiectasis in severe asthma: Clinical features and outcomes	Research article
Mao B, Yang JW, Lu HW, Xu JF	2016	Asthma and bronchiectasis exacerbation	Original article
Luján M, Gallardo X, et al.	2013	Prevalence of bronchiectasis in asthma according to oral steroid requirement: Influence of immunoglobulin levels	Clinical study
Truong T	2013	The overlap of bronchiectasis and immunodeficiency with asthma	Review article
Oguzulgen IK, Kervan F, Ozis T, Turktas H	2007	The impact of bronchiectasis in clinical presentation of asthma	Clinical report
Kang HR et al.	2014	The effects of bronchiectasis on asthma exacerbation	Original article
Huang YJ	2015	The respiratory microbiome and innate immunity in asthma	Review article
Huang YJ, Boushey HA	2015	The microbiome in asthma	Review and feature article
Chang HS et al.	2017	Neutrophilic inflammation in asthma: Mechanisms and therapeutic considerations	Review article
Whitters D, Stockley R	2012	Immunity and bacterial colonization in bronchiectasis	Review article
Chalmers JD, Chotirmall SH	2018	Bronchiectasis: New therapies and new perspectives	Review article
Porsbjerg C, Menzies-Gow A	2017	Co-morbidities in severe asthma: Clinical impact and management	Review article
García-Clemente M, Enríquez-Rodríguez AI, et al.	2020	Severe asthma and bronchiectasis	Original article
Carpagnano GE, Scioscia G, Lacedonia D, Curradi G, Barbaro MP	2019	Severe uncontrolled asthma with bronchiectasis: A pilot study of an emerging phenotype that responds to mepolizumab	Original research
Gao YH et al.	2016	Aetiology of bronchiectasis in adults: A systematic literature review	Systematic review
Henkle E et al.	2019	Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis	Original article
Rademacher J, Konwert S, et al.	2020	Anti-IL5 and anti-IL5Rα therapy for clinically significant bronchiectasis with eosinophilic endotype: A case series	Research letter
Brusselle GG, Joos G	2014	Is there a role for macrolides in severe asthma?	Review article
Sears MR	2014	Trends in the prevalence of asthma	Commentary
GINA†	2021	Global Strategy for Asthma Management and Prevention	Guidelines

*ERS: European Respiratory Society, †GINA: Global Initiative for Asthma

This is of greatest importance in severe asthma cases, in recurrent infectious exacerbators, or in those not responding to standard therapy despite the optimal management. The suspicion of BE is also raised by the chronic chough/sputum ratio, the history of pneumonia, the evidence of neutrophilia, or *Aspergillus* sensitization.[6]

The data about the impact of BE on asthma are scarce since most asthma clinical studies are excluding those with coexisting BE.[31] The recent systematic review with meta-analysis of Zhang and colleagues, including five observational studies with 839 patients, highlighted that those with asthma and comorbid BE are older than patients with asthma alone, with no significant difference regarding sex, smoking history, and duration of asthma.[3] Some of these findings were also observed in the study of Luján et al.,[27] where patients with asthma-associated BE were older and with longer-term asthma history compared with non-asthma-associated BE.

In clinical terms, the presence of chronic expectoration and purulent sputum in asthmatic patients highlights the importance to take into consideration the possible coexistence of BE. They not only are independent risk factors for the presence of BE but also correlate with chronic potentially pathogenic microorganisms (PPMs) colonization and antibiotic use.[2] Unfortunately, only a few studies focused on the data of chronic PPMs;[3] therefore this direction needs to be further explored.

Furthermore, patients with asthma and BE overlap have a poorer control, with increased asthma severity and severe and difficult-to-control asthma forms, higher exacerbation rate (in the previous year), and pulmonary complications, compared with patients with asthma alone.[3,24,32]

As contributing factors for these findings, more severe airflow obstruction and airway remodeling, oxidative stress,[33] a well-known contributor to the pathogenesis of different chronic diseases,[34,35] and mucus hypersecretion with subsequent formation of mucous plugs are closely related to asthma exacerbation in asthmatics with coexistent BE.[3,36,37]

In addition, the role of persistent bacterial airway colonization with a neutrophil-predominated inflammation and an active neutrophil elastase and protease pattern is an important risk factor for asthma exacerbation in patients with asthma and BE.[3,38,39]

Bronchiectasis with comorbid asthma

The prevalence of asthma in patients with BE has a large variability ranging from 2.7% to 42% depending on patient selection and type or severity of asthma.[3,9,19–21,31] Smoking history is an underlying common condition in several diseases, including asthma and BE.[40,41]

Although the influence of asthma on BE remains ambiguous, some evidence suggests a new phenotype of BE in the case of patients with BE and asthma.[21] According to a study by Ferri et al.,[9] compared with patients with BE alone, those with BE and coexistent asthma seem to be younger and show a significant association with atopy, chronic rhinosinusitis, or fractional exhaled nitric oxide (FeNO) levels, well known asthma-related features.

The presence of asthma is associated with an increased risk of BE exacerbation in patients with noncystic fibrosis BE.[21] Mao and colleagues reported that BE patients with coexistent asthma were 2.6 times more likely to suffer BE exacerbation than those without asthma, independent of other variables.[21] Ferri et al.[9] recently confirmed this finding and reported an independent increase in the risk of BE exacerbation in asthmatics with coexistent BE despite higher Bhalla score and lower Bronchiectasis Severity Index (BSI) compared with patients without asthma. The Bhalla score is used to assess the radiological severity of BE, with a maximum score of 25, and is inversely correlated with the radiological severity.[42] The BSI is a multidimensional scoring system used to assess the clinical severity, with an excellent predictive index for exacerbations, hospital admissions, and mortality.[43]

The main factors that may play a role in BE exacerbations are mucus hypersecretion, oxidative stress, airway remodeling, and microorganisms isolated from the lower respiratory airway of asthma patients.[36,37] *Pseudomonas aeruginosa* isolation from sputum samples is the major recognized independent risk factor for disease severity and exacerbation.[9]

Bronchiectasis and difficult-to-control severe asthma

Severe asthma may encounter in approximately 10% of asthma patients, and around 5% of these patients present difficult-to-control severe asthma.[24] Besides the overall

increased health-related costs, morbidity and mortality are higher, with 20 times greater risk for presentation in the emergency room and hospitalization compared with the less severe forms.[24]

The overlap between BE and severe asthma has consistent research evidence.[28] Moreover, the association between severe asthma and BE may be seen as an emerging phenotype.[44]

The prevalence of BE is more increased in severe asthma, with a range between 24% and 47%, compared with 3% in mild asthma.[17,24,45,46] It looks like almost a third of patients with uncontrolled moderate-to-severe asthma present concomitant BE.[2]

Though both diseases were classically related to the presence of allergic bronchopulmonary aspergillosis (ABPA), in the last years, the data showed an increased prevalence (30%) of BE in severe asthma even in the absence of ABPA.[2,46] The most prevalent BE is cylindrical (more than 90%) and bilateral, predominantly in the lower lobes.[2] Patients sharing both conditions are presenting a higher rate of pulmonary complications and hospitalization with respiratory failure.[20]

According to the systematic literature review of Gao and colleagues, in patients with severe asthma, BE increases the hospitalization rate with an odds ratio OR=2.09 compared with asthma without BE.[47]

In terms of prognosis, even the data for patients with asthma and BE are still narrow; those with severe asthma and BE overlap seem to be worse (clinical and exacerbation rate) compared with asthmatics without BE.[6,16,48]

Allergy biomarkers in asthma-bronchiectasis overlap

Regarding the blood eosinophil levels, they were significantly higher in patients with comorbid asthma and BE versus asthma alone (p=0.03).[3] The same finding was also observed when patients with BE and asthma were compared with those with BE alone.[9]

The impact on serum IgE levels was not found when compared patients with comorbid asthma and BE with patients without BE.[3]

Functional features of asthma-bronchiectasis overlap

Airway obstruction, in terms of postbronchodilator FEV_1/FVC ratio, is significantly more reduced in patients with comorbid asthma and BE when compared with patients with asthma alone according to the recent meta-analysis of Zhang and colleagues.[3] Lower FEV_1 and FEV_1/FVC values were also noticed in patients with asthma-associated BE compared with non-asthma-associated BE.[27]

Furthermore, the results of Mao et al.[21] showed that patients with BE and coexisting asthma have poorer small airway function than those with BE without asthma.

The FeNO measurement, with a cut-off point of 22.5 ppb (parts per billion) may be a good biomarker to distinguish asthma in BE patients, from those with BE but no asthma as suggested by Chen et al.[1] These results were consistent with those of Padilla-Galo et al.[2] In their prospective study on 398 patients, the optimal FeNO cut-off of 20.5 ppb was used to differentiate asthmatics with BE from patients without BE.[2] Moreover, Padilla-Galo et al.[2] proposed the NOPES score, an easy-to-use scoring system with a high prognostic value for BE in uncontrolled moderate-to-severe asthma patients. The variables used for this score are FeNO, pneumonia, expectoration, and asthma severity. A high score (range 0–4) is related to a higher probability of BE in patients with uncontrolled moderate-to-severe asthma.

Still, further large-scale prospective studies are required for validation of the FeNO, the NOPES score, or other useful tools.[1,6,49–51]

Concerns and perspectives regarding the treatment of the duo asthma-bronchiectasis

In patients with asthma, inhaled corticosteroids (ICS) are the cornerstone of pharmacological management.[29,52] On the other hand, the latest European Respiratory Society guidelines[6] do not recommend the use of ICS in patients with BE, mainly because they seem to be involved in promoting a bacterial load, with consequent impact on exacerbations.[6,9,53] Still, if asthmatics are already on ICS treatment, the coexistence of BE alone is

not a criterion for ICS withdrawal.[6,7] In patients with severe asthma and BE, the response to asthma treatment is poorer, and long-term antibiotics and thoracic physiotherapy, as used in the management of BE, are frequently needed.[6]

A higher blood eosinophil count in patients with BE and concomitant asthma compared with BE or asthma alone is suggestive for a type 2 endotype inflammation and raises relevant implications on the treatment perspectives.[9] Although limited clinical cases are currently reported in the literature, the target for new biological anti-interleukin 5 (IL-5) drugs in patients with BE and coexistent asthma is promising.[9,44,54]

Long-term therapy with macrolides may be considered when asthma, particularly the severe phenotype, coexists with BE. Antibiotics can reduce the bacteria overload, bronchial inflammation, and exacerbation rate both in patients with BE and asthma.[3] The treatment is effective and well tolerated.[4,55]

Final considerations

The increased interest in the scientific community for patients with asthma-BE overlap is multidimensional, targeting important knowledge gaps on pathophysiology, inflammatory features, risk factors, clinical phenotype, or prognosis. The need to timely and accurately recognize the presence of both conditions, to define specific therapeutic tools for each condition, and to choose the optimal management approach and follow-up interventions in patients with asthma-BE overlap remain goals for both research and clinical practice.

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