



# Bronchiectasis and asthma: a dangerous liaison?

*Claudia Crimi, Sebastian Ferri, and Nunzio Crimi*

## Purpose of review

To explore the latest insight of the literature on the asthma/bronchiectasis phenotype providing an updated overview about epidemiological, clinical and biological evidence linking these two conditions.

## Recent findings

An increasing body of literature has shown that the association of asthma and bronchiectasis is a frequent phenomenon leading to a more severe disease with frequent exacerbations. The mechanisms by which the two diseases are linked are still not well established but they share several clinical and immunological features and many comorbidities.

## Summary

The early identification of bronchiectasis through high-definition computer tomography in patients with severe asthma is crucial in order to provide an adequate treatment for both diseases and therefore to better control symptoms, exacerbations and infections.

## Keywords

asthma, bronchiectasis, infections

## INTRODUCTION

Asthma is a complex and heterogeneous disease characterized by chronic airway inflammation that determines a variable airflow limitation, which leads to respiratory symptoms such as cough, wheezing, chest tightness and dyspnea of various intensities [1].

In the latest document of Global initiative for Asthma 2018 [1], it was reiterated that the primary goal for achieving control of asthmatic patients is based on verification of adherence to therapy and on identification and management of comorbidities [2]. The latter are of various types determining a great variability of asthma presentation, and the lack of their recognition often explains the therapeutic failure and the worsening of symptoms with more frequent exacerbations, a greater disease severity and higher healthcare costs [3<sup>••</sup>].

In recent years, increasing efforts were made by the scientific community in an attempt to identify subgroups of patients with similar characteristics in terms of symptoms, exacerbations, airway inflammation, response to treatment and prognosis, as the early recognition of 'asthma clinical phenotypes' [4] is crucial for providing an adequate therapeutic intervention tailored to the single patient based on his predict response or risk of disease (precision therapy) [5]. Numerous clinically relevant phenotypes were described so far but the clinical phenotyping, at least for severe refractory asthma, is still inadequate,

probably because phenotypes description has not been fully matched by endotype discovery [3<sup>••</sup>]. Nevertheless, in the systematic evaluation of patient with potentially severe asthma, it is fundamental to differentiate between true severe refractory asthma and patients with difficult to control asthma in whom symptoms are mainly because of comorbidities [6].

## DEFINITION

Cough, sputum, dyspnea and frequent exacerbations are clinical symptoms typical of asthma but they can also occur in patients affected by bronchiectasis.

Bronchiectasis is a progressive and complex disease characterized by an abnormal and irreversible widening of the bronchi that results in a decreased clearance of respiratory secretions that leads to airflow obstruction and increased mucus production, increasing the risk of respiratory infections that may determine an inflammatory injury which promote

Respiratory Medicine Unit, A.O.U. 'Policlinico-Vittorio Emanuele', Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Correspondence to Nunzio Crimi, MD, Respiratory Medicine Unit, A.O.U. 'Policlinico - Vittorio Emanuele', Department of Clinical and Experimental Medicine, University of Catania, Via S. Sofia, 78, 95123 Catania, Italy. Tel/fax: +0953781423; e-mail: crimi@unict.it

**Curr Opin Allergy Clin Immunol** 2019, 19:46–52

DOI:10.1097/ACI.0000000000000492

## KEY POINTS

- Asthma and bronchiectasis have several symptoms in common and share several comorbidities and eziopathological mechanism.
- The overlap between the two diseases may result in a more severe disease with frequent exacerbations.
- High-definition computer tomography should be considered in patients with severe asthma and frequent exacerbations to rule out the copresence of bronchiectasis.
- Tailored treatment of both diseases is crucial for symptoms control and prevention of chronic infections.

the persistent colonization of pathogens in the affected bronchi as well as denude the airways of mucociliary structures that provide clearance of secretions [7].

The copresence of bronchiectasis and asthma is a not so rare combination of overlapping symptoms and frequent exacerbations but is also one of the least considered, not even the GINA guidelines [1] take it into account when highlighting asthma clinical phenotype and comorbidities.

Nevertheless, the recognition of coexistence of bronchiectasis in patients with chronic airway diseases and particularly with asthma is very important as it changes the management and follow-up of asthma alone especially in terms of exacerbations and disease severity [8<sup>\*\*\*</sup>].

Considering that asthma and bronchiectasis may coexist in many patients, a causality dilemma remains as it is unclear whether asthma is a consequence of bronchiectasis or, rather, bronchiectasis is an underlying cause of asthma, so which came first, the chicken or the egg? This is still an answered question.

## EPIDEMIOLOGY: PREVALENCE OF BRONCHIECTASIS IN ASTHMA

Recently, several studies have tried to estimate the real frequency of bronchiectasis in bronchial asthma but the existing evidence is still conflicting and the estimation of bronchiectasis frequency in asthma remains wide, ranging between 0.8 and 67% [3<sup>\*\*\*</sup>,9<sup>\*\*\*</sup>,10,11<sup>\*\*\*</sup>], in contrast the prevalence of asthma in patients affected by bronchiectasis is accounted only for 3–7% [12].

A real-life US data registry reported a clinical diagnosis of asthma in 29% of patients with bronchiectasis, but less than 5% of patients had a confirmed diagnosis of asthma [13<sup>\*</sup>], whereas the latter

was reported as the cause of bronchiectasis in 5.4% of patients in a Spanish Registry Study and was correlated to poorer lung function but less chronic bronchial infection [14].

In a recent study, Padilla-Gallo *et al.* [9<sup>\*\*\*</sup>] investigated the prevalence of bronchiectasis in a large cohort of 398 nonsmokers with uncontrolled moderate-to-severe asthma, showing a prevalence of 28.4% in these patients; 20.6% of the patients with moderate asthma were diagnosed with bronchiectasis, whereas the prevalence was higher in patients with severe asthma (33.6%).

This wide variability is mainly because of the heterogeneity of the published studies [3<sup>\*\*\*</sup>,9<sup>\*\*\*</sup>,10,11<sup>\*\*\*</sup>,12] including the use of different radiological methods for bronchiectasis detection, lack of data on asthma severity when there is copresence of bronchial dilatations, retrospective design and small sample size. We cannot also exclude that clinical signs of bronchiectasis are overlooked in patients with similar pulmonary symptoms like asthma, thanks to the diffusion and reliability of high-definition computer tomography [4] that is able to accurately identify minimal structural changes, nevertheless it is well established that patients with bronchiectasis per se are complex, have an increased mortality [15], tend to have an annual 8% increase in ICU admission with a high ICU and in-hospital mortality [16].

The way the two diseases affect each other remains unclear, but the ever more frequent findings of bronchiectasis in patients with bronchial asthma, often severe and long lasting, have generated the hypothesis that asthma can play a causative role in the development of bronchiectasis [17,18]; however, there is also a large number of patients with clinically relevant bronchiectasis who may develop asthma-like symptoms [12]; all these aspects make diagnosis, disease management and understanding of which of the two diseases caused the other, a real challenge.

However, undoubtedly, the published studies [3<sup>\*\*\*</sup>,11<sup>\*\*\*</sup>] confirmed the quite frequent association between asthma and bronchiectasis, defining a true clinical–radiological phenotype, characterized by a worse symptomatology and frequent exacerbations as shown in Table 1.

## IMPACT OF BRONCHIECTASIS ON ASTHMA AND VICE VERSA: CLINICAL ASPECTS

Recent findings [8<sup>\*\*\*</sup>] confirmed that patients with asthma and copresence of bronchiectasis are older, have a more severe disease, a nonallergic cause, persistent asthma often refractory to conventional

**Table 1.** Characteristics of patients with asthma and bronchiectasis

|                                                                    |     |
|--------------------------------------------------------------------|-----|
| Age                                                                | +++ |
| Duration of asthma                                                 | +++ |
| Smoking history                                                    | +   |
| Allergy history                                                    | +   |
| Allergy to <i>Aspergillus</i> and molds                            | +   |
| Bronchial obstruction                                              | +++ |
| Bronchial reversibility                                            | +   |
| Sputum production                                                  | +++ |
| Mucus purulence                                                    | +++ |
| Pathogens in sputum ( <i>P. aeruginosa</i> , ( <i>Hemophilus</i> ) | +++ |
| Frequent exacerbations                                             | +++ |
| Frequent use of antibiotics                                        | +++ |
| Uncontrolled asthma                                                | +++ |
| Steroids resistance                                                | +++ |
| FeNO > 20 ppb                                                      | +   |
| Sputum eosinophils                                                 | +   |
| Sputum neutrophils                                                 | +++ |
| GERD                                                               | +++ |
| Chronic rhinosinusitis                                             | +++ |
| Immune deficiency                                                  | ++  |
| Response to macrolides                                             | ++  |
| Previous pneumonia                                                 | +++ |

FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux; ppb, parts per billion.

treatment with a higher risk of exacerbations, infections and hospitalization for respiratory failure. Moreover, asthma and bronchiectasis not only share similar clinical symptoms (cough, sputum and dyspnea) but also similar underlying cause and extrapulmonary comorbidities, as both are associated with rhinosinusitis, gastroesophageal reflux disease (GERD), allergic bronchopulmonary aspergillosis (ABPA), immunodeficiency, infections, good clinical response to macrolides and more exacerbations.

### Chronic rhinosinusitis

Several studies have demonstrated that both allergic and nonallergic lower and upper airway diseases not only coexist but are also pathogenically linked leading to the concept of the 'united airways', with the inflammatory response originating in the upper airway and expanding to the lower airway. This association is particularly true for allergic rhinitis and chronic rhinosinusitis (CRS) and both asthma and bronchiectasis.

A recent Italian registry of patients with severe uncontrolled asthma has shown that sinusitis is observed in 37.9% of patients with severe asthma,

GERD in 42.1% and bronchiectasis in 13.9% of patients [19]; the prevalence of CRS ranges from 22 to 42% and it is higher (45%) in patients with severe asthma [20<sup>22</sup>].

A recent study found a significantly higher prevalence (35%) of CRS among patients with bronchiectasis than the prevalence of 2–5.5% reported in the general population [8<sup>21</sup>].

### Gastroesophageal reflux disease

Chronic aspiration of oropharyngeal or gastric contents may contribute to or result in both bronchiectasis and asthma. GERD symptoms are present in 30–90% of asthmatic patients [20<sup>22</sup>], but it is very also common in patients with bronchiectasis ranging from 26 to 75% [3<sup>23</sup>], particularly in those with non-tuberculous mycobacteria infection [13<sup>23</sup>] and it has been associated with poor disease control and increased risk of exacerbation in both diseases [24<sup>25</sup>].

### Response to macrolides

Recent controlled trials have provided evidence that macrolide antibiotics can reduce exacerbation rates in individuals with asthma [25] as well as in individuals with noncystic-bronchiectasis [26]. The AZISAST study [27] compared azithromycin 250 mg and placebo given three times per week for 26 weeks in asthma patients with a history of frequent exacerbations or frequent lower respiratory tract infection or both, showing a reduction in exacerbations in patients with noneosinophilic asthma. In a recent randomized controlled trial (AMAZES), Gibson *et al.* [28] have shown that adding oral azithromycin 500 mg, three times per week, for 48 weeks in patients with symptomatic asthma despite treatment with inhaled corticosteroid and a long-acting bronchodilator with no history of frequent exacerbation was able to decrease asthma exacerbations' frequency in both eosinophilic and noneosinophilic asthma and reduce respiratory infections improving health-related quality of life (QoL). Similarly, in patients with bronchiectasis, a recent Cochrane systematic review of 11 studies on the long-term use of macrolides has shown a reduced frequency of exacerbations and improved QoL [26].

### Allergic bronchopulmonary aspergillosis

The copresence of asthma and bronchiectasis is also very common in ABPA, which is an allergic condition determined by a hypersensitivity response of the immune system to the colonization of the airways by fungus *Aspergillus fumigatus* characterized by mucus accumulation in the bronchial lumen,

bronchiectasis, pulmonary infiltrates and uncontrolled asthma. Nearly, 25% of asthmatic patients are sensitized to *A. fumigatus* antigen but the prevalence of the disease is about 1% in asthmatic patients raising up to 5% in patients with severe asthma and of 0–11% of patients with bronchiectasis [29]. Recently, it has been shown that in asthmatic patients with bronchiectasis, in the absence of sufficient criteria of ABPA, the increased IgE levels could be due to fungal colonization or infection [30], strengthening the relationship between bronchiectasis and fungi-sensitized asthma.

### Immunodeficiency

The concomitant presence of immunodeficiency is common in patients with bronchiectasis, increasing the susceptibility to recurrent or persistent infections and bronchial wall inflammation, hence additional examination to rule out the presence of immune deficiency in these patients is recommended by international guidelines [7]. A recent study [31] investigated the association of primary immune deficiency and chronic respiratory disorders, suggested that not only bronchiectasis, but also asthma represents a common complication (33–47%) of immune deficiency diseases, therefore in the presence of long-lasting asthma symptoms and frequent infections, an underlying antibody deficiency should be investigated. Even though, it has to be considered that any severe asthma patients has been treated with systemic corticosteroids, which can determine a decrease in immunoglobulin levels. Interestingly, Lujan *et al.* [32] showed that steroid-dependent asthma patients have an increased risk of developing bronchiectasis (15%) compared to asthma patients not treated with corticosteroids (4%) and this was because of a higher severity of the disease resulting from a more severe inflammatory level, bronchial remodeling and impairment of mucociliary clearance.

### Exacerbations

The presence of bronchiectasis per se is a risk factor for asthmatic exacerbation as the reduction of mucociliary clearance and hypersecretion of mucus contribute to worsening the airflow obstruction caused by the mucus itself, which can act as an asthma trigger [11<sup>¶</sup>]. Moreover, asthmatic patients with bronchiectasis may be treated with ‘excessive therapy’ and considered to have symptoms refractory to the ‘conventional’ asthma treatment. Furthermore, bronchiectasis can contribute to severe pulmonary complications in asthmatic patients like chronic respiratory failure. Moreover, as bronchiectasis is a

complex chronic disease, a multidisciplinary with specialists to develop an individualized patient management plan would provide advanced planning should the patient’s condition worsen [33].

### INFLAMMATORY RESPONSE AND MECHANISM INVOLVED IN ASTHMA WITH BRONCHIECTASIS

The exact pathophysiological mechanism involved in the genesis of bronchiectasis in patients with asthma is still unknown, and this is mainly because of the lack of animal models to study the cause of this disease [34], even though asthma and bronchiectasis shared several inflammatory mechanisms that may influence one disease to the other. It is well recognized that eosinophilic inflammation is the most commonly described inflammatory phenotype in patients with asthma; however, a subset of patients with neutrophil-dominated inflammation has also been identified [35]. The neutrophilic airway inflammation has been associated with severe asthma in the context of nontype 2 inflammation; however, neutrophils have been also detected in the airways of allergic asthmatic patients, especially during exacerbations [36]. Hence, while neutrophils have an important role in pathogen elimination, the presence of persistent neutrophilia and the associated production of chemokines and proteases may determine airway injury and obstruction, mucus hypersecretion and airway remodeling (Fig. 1). Notably, high sputum neutrophil counts showed to be associated with a poor response to treatment with inhaled corticosteroids, with a greater disease severity [36], differences in microbiota composition that may increase the risk of lung infections [37] and recurrent infections [38]. An excessive neutrophilic airways inflammation is also typical of bronchiectasis; Tsikrika *et al.* [39] have recently shown in a small cohort of patients with bronchiectasis that those with neutrophilic inflammation in the sputum showed greater radiological severity, a more pronounced level of IL-8 in sputum supernatant, a lower bronchodilator reversibility and chronic colonization of *Pseudomonas aeruginosa*, conversely patients with eosinophilic inflammation in the sputum are characterized by a greater level of FeNO and IL-13 in sputum supernatant and a greater degree of bronchial obstruction. In a recent Spanish study [9<sup>¶</sup>], a score called NOPES (FeNO, Pneumonia, Expectoration, Severity) was developed with the aim of predicting the presence of bronchiectasis in patients with asthma and based on the FeNO value (FeNO < 20.5 ppb) the score is able to discriminate among three groups of patients based on the presence of previous pneumonia, the presence of daily

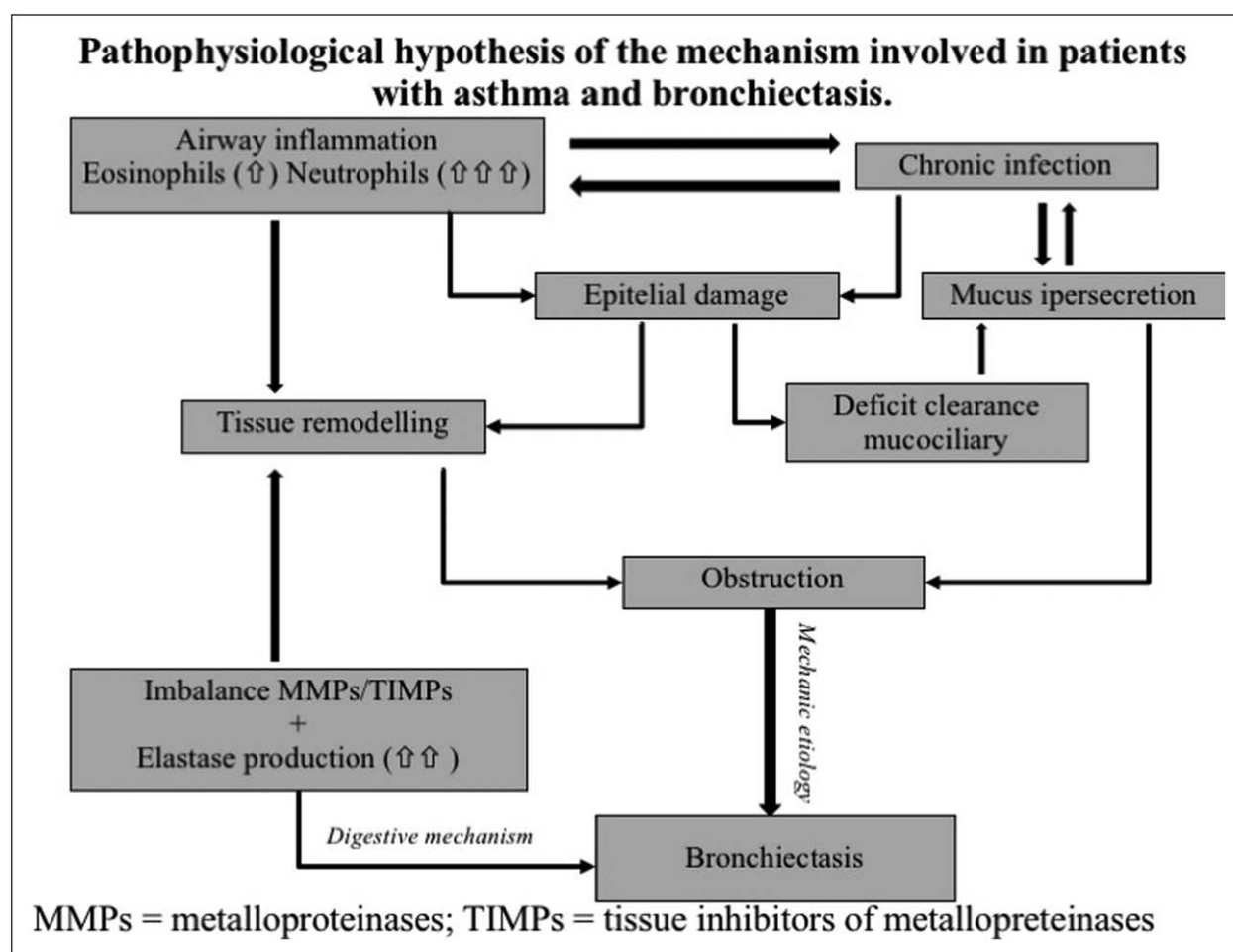


**FIGURE 1.** Pathophysiological hypothesis of the mechanism involved in patients with asthma and bronchiectasis.

expectorations and severity of asthma with a good specificity (95%), a negative predictive value of 76% and a positive predictive value of 67% for NOPES value more than 2. Moreover, in both diseases, an increased activity of neutrophil elastase and greater level of matrix metalloproteinase 9 have been reported [40,41], and are responsible of lung tissue damage and remodeling. Less attention has been paid by the scientific community on the variant of asthma with bronchial hypersecretion; recent findings showed that this subset of patients has a more severe and uncontrolled disease [42], with poor QoL as well as a predominantly nonallergic inflammatory phenotype. Crespo-Lessmann *et al.* [43] showed that hypersecretory asthmatic patients were older, had greater disease severity, increased bronchial obstruction, use greater doses of inhaled steroids, have a higher proportion of nasal polyposis, less asthma control, lower QoL, a greater number of emergency room visits and a greater need for short courses of oral corticosteroids in the previous year, negative prick test, lower levels of IgE, lower

albumin levels in peripheral blood and lower levels of lymphocytes. Moreover, a strong inverse relationship between mucus plugs score based on visual assessment of multidetector computed tomography scans and FEV1 values [44] was found, confirming that hypersecretions may worsen airflow obstruction and become a trigger of asthma [11<sup>11</sup>].

## CONCLUSION

It is still unclear whether asthma is a consequence of bronchiectasis or, rather, bronchiectasis is an underlying cause of asthma.

Nevertheless, the association of the two diseases will have clinical implications for more frequent chronic infections and disease severity. Therefore, a high-definition computer tomography scan of the thorax must be performed in all patients with severe asthma complaining chronic cough with sputum, frequent exacerbations, in order to eventually identify bronchiectasis. If asthma and bronchiectasis coexist, patients must receive treatment for both

diseases, not only pharmacological therapy but also physiotherapy [45], to promote drainage and expectoration in order to control symptoms and infections.

## Acknowledgements

None.

## Financial support and sponsorship

None.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Bateman ED, Hurd SS, Barnes PJ, *et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31:143–178.
2. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017; 377:965–976.
3. Coman I, Pola-Bibian B, Barranco P, *et al.* Bronchiectasis in severe asthma: ■ clinical features and outcomes. *Ann Allergy Asthma Immunol* 2018; 120:409–413.
4. Kim S, Nam Jin K, Cho SH, *et al.* Severe asthma phenotypes classified by site of airway involvement and remodeling via chest CT scan. *J Investig Allergol Clin Immunol* 2018; 28:312–320.
5. Agustí A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47:410–419.
6. Colodenco D, Palomares O, Celis C, *et al.* Moving toward consensus on diagnosis and management of severe asthma in adults. *Curr Med Res Opin* 2018; 34:387–399.
7. Polverino E, Goeminne PC, McDonnell MJ, *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629.
8. Polverino E, Dimakou K, Hurst J, *et al.* The overlap between bronchiectasis ■ and chronic airway diseases: state of the art and future directions. *Eur Respir J* 2018; 52: 1800328.

Overview of current available evidence on the association of bronchiectasis and chronic respiratory diseases, outlining definition, clinical aspects and management.

9. Padilla-Galo A, Oliveira C, Fernandez de Rota-Garcia L, *et al.* ■ Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: a study in 398 patients. *Respir Res* 2018; 19:43.

This article identified the prevalence of bronchiectasis in patients with uncontrolled asthma and developed a prognostic score to identify risk factors associated with bronchiectasis.

10. Weatherburn CJ, Guthrie B, Mercer SW, Morales DR. Comorbidities in adults with asthma: population-based cross-sectional analysis of 1.4 million adults in Scotland. *Clin Exp Allergy* 2017; 47:1246–1252.
11. Dimakou K, Gousiou A, Toubis M, *et al.* Investigation of bronchiectasis in ■ severe uncontrolled asthma. *Clin Respir J* 2018; 12:1212–1218.
12. Polverino E, Aliberti S, Blasi F, Haworth C, Elborn S, Loebinger M, Menendez R, De Soyza A, Ringhausen F, Welte T, Torres A, Wilson R, Dimakou K, Chalmers J. Self-reported asthma as a co-morbidity of bronchiectasis in the EMBARC registry. Second World Bronchiectasis congress; Milan, 6–8 July 2017. *2017*.
13. Aksamit TR, O'Donnell AE, Barker A, *et al.* Adult patients with bronchiectasis: ■ a first look at the US Bronchiectasis Research Registry. *Chest* 2017; 151:982–992.

The article described the clinical, radiological and microbiological characteristics of patients with bronchiectasis.

14. Oliveira C, Padilla A, Martinez-Garcia MA, *et al.* Etiology of bronchiectasis in a cohort of 2047 patients. An analysis of the Spanish Historical Bronchiectasis Registry. *Arch Bronconeumol* 2017; 53:366–374.
15. Quint JK, Millett ER, Joshi M, *et al.* Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016; 47:186–193.
16. Navaratnam V, Muirhead CR, Hubbard RB, De Soyza A. Critical care admission trends and outcomes in individuals with bronchiectasis in the UK. *QJM* 2016; 109:523–526.
17. Lonni S, Chalmers JD, Goeminne PC, *et al.* Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. *Ann Am Thorac Soc* 2015; 12:1764–1770.
18. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. *Respirology* 2017; 22:651–661.
19. Maio S, Baldacci S, Bresciani M, *et al.* RItA: the Italian severe/uncontrolled asthma registry. *Allergy* 2018; 73:683–695.
20. Tay TR, Hew M. Comorbid 'treatable traits' in difficult asthma: current ■ evidence and clinical evaluation. *Allergy* 2018; 73:1369–1382.
21. Shteinberg M, Nassrallah N, Jrbashyan J, *et al.* Upper airway involvement in bronchiectasis is marked by early onset and allergic features. *ERJ Open Res* 2018; 4: 00115-2017.
22. Broers C, Tack J, Pauwels A. Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. *Aliment Pharmacol Ther* 2018; 47:176–191.
23. Kang JB, Lee DH, Kwon SH, *et al.* The prevalence of nontuberculous mycobacterial lung disease with or without reflux esophagitis. *Korean J Gastroenterol* 2018; 71:18–23.
24. Denlinger LC, Phillips BR, Ramratnam S, *et al.* Inflammatory and comorbid ■ features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med* 2017; 195:302–313.
25. Kew KM, Undela K, Kotorts I, Ferrara G. Macrolides for chronic asthma. *Cochrane Database Syst Rev* 2015; (9):CD002997.
26. Kelly C, Chalmers JD, Crossingham I, *et al.* Macrolide antibiotics for bronchiectasis. *Cochrane Database Syst Rev* 2018; 3:CD012406.
27. Hahn DL, Grasmick M, Hetzel S, *et al.* Azithromycin for bronchial asthma in adults: an effectiveness trial. *J Am Board Fam Med* 2012; 25:442–459.
28. Gibson PG, Yang IA, Upham JW, *et al.* Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; 390:659–668.
29. Aliberti S, Masfield S, Polverino E, *et al.* Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *Eur Respir J* 2016; 48:632–647.
30. Rai G, Ansari MA, Dar SA, *et al.* Serum cytokine profile in patients with chronic rhinosinusitis with nasal polyposis infected by *Aspergillus flavus*. *Ann Lab Med* 2018; 38:125–131.
31. Berger M, Geng B, Cameron DW, *et al.* Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease. *Respir Med* 2017; 132:181–188.
32. Lujan M, Gallardo X, Amengual MJ, *et al.* Prevalence of bronchiectasis in asthma according to oral steroid requirement: influence of immunoglobulin levels. *Biomed Res Int* 2013; 2013:109219.
33. Chalmers JD, Sethi S. Raising awareness of bronchiectasis in primary care: overview of diagnosis and management strategies in adults. *NPJ Prim Care Respir Med* 2017; 27:18.
34. Amati F, Franceschi E, Gramegna A, *et al.* Investigating the etiology of bronchiectasis: you do not find what you do not look for. *Respiration* 2017; 93:228–229.
35. Wenzel SE, Schwartz LB, Langmack EL, *et al.* Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999; 160:1001–1008.
36. Chang HS, Lee TH, Jun JA, *et al.* Neutrophilic inflammation in asthma: mechanisms and therapeutic considerations. *Expert Rev Respir Med* 2017; 11:29–40.
37. Taylor SL, Leong LEX, Choo JM, *et al.* Inflammatory phenotypes in patients with severe asthma are associated with distinct airway microbiology. *J Allergy Clin Immunol* 2018; 141:94–103; e15.
38. Simpson JL, Grissell TV, Douwes J, *et al.* Innate immune activation in neutrophilic asthma and bronchiectasis. *Thorax* 2007; 62:211–218.
39. Tsirikas S, Dimakou K, Papaioannou AI, *et al.* The role of noninvasive modalities for assessing inflammation in patients with noncystic fibrosis bronchiectasis. *Cytokine* 2017; 99:281–286.
40. Polverino E, Rosales-Mayor E, Dale GE, *et al.* The role of neutrophil elastase inhibitors in lung diseases. *Chest* 2017; 152:249–262.
41. Gorska K, Paplinska-Goryca M, Nejman-Gryz P, *et al.* Eosinophilic and neutrophilic airway inflammation in the phenotyping of mild-to-moderate asthma and chronic obstructive pulmonary disease. *COPD* 2017; 14:181–189.

42. Martinez-Rivera C, Crespo A, Pinedo-Sierra C, *et al.* Mucus hypersecretion in asthma is associated with rhinosinusitis, polyps and exacerbations. *Respir Med* 2018; 135:22–28.
43. Crespo-Lessmann A, Mateus E, Torreon M, *et al.* Asthma with bronchial hypersecretion: expression of mucins and toll-like receptors in sputum and blood. *J Asthma Allergy* 2017; 10:269–276.
44. Dunican EM, Elicker BM, Gierada DS, *et al.* Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest* 2018; 128:997–1009.
45. Shen Y, Huang S, Kang J, *et al.* Management of airway mucus hypersecretion in chronic airway inflammatory disease: Chinese expert consensus (English edition). *Int J Chron Obstruct Pulmon Dis* 2018; 13:399–407.