



Impact of asthma on bronchiectasis severity and risk of exacerbations

Sebastian Ferri , Claudia Crimi , Raffaele Campisi , Giulia Cacopardo , Giovanni Paoletti , Francesca Puggioni , Nunzio Crimi & Enrico Heffler

To cite this article: Sebastian Ferri , Claudia Crimi , Raffaele Campisi , Giulia Cacopardo , Giovanni Paoletti , Francesca Puggioni , Nunzio Crimi & Enrico Heffler (2020): Impact of asthma on bronchiectasis severity and risk of exacerbations, Journal of Asthma, DOI: [10.1080/02770903.2020.1857395](https://doi.org/10.1080/02770903.2020.1857395)

To link to this article: <https://doi.org/10.1080/02770903.2020.1857395>



Published online: 09 Dec 2020.



Submit your article to this journal [↗](#)



Article views: 11



View related articles [↗](#)



View Crossmark data [↗](#)



Impact of asthma on bronchiectasis severity and risk of exacerbations

Sebastian Ferri, MD^{a,b} , Claudia Crimi, MD, PhD^c , Raffaele Campisi, MD^c , Giulia Cacopardo, MD^c, Giovanni Paoletti, MD^{a,b} , Francesca Puggioni, MD^{a,b} , Nunzio Crimi, MD^c , and Enrico Heffler, MD, PhD^{a,b} 

^aPersonalized Medicine, Asthma and Allergy, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; ^bDepartment of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; ^cRespiratory Diseases and Pulmonary Rehabilitation, Policlinico Universitario di Catania, Catania, Italy

ABSTRACT

Objective: Asthma is a frequent comorbidity of bronchiectasis, with possible implications for exacerbation and severity. We investigated the clinical impact of asthma on bronchiectasis in terms of disease severity and exacerbation risk.

Methods: We collected demographic, clinical, and functional characteristics of patients with a confirmed diagnosis of bronchiectasis. All patients were investigated for concomitant diagnosis of asthma. The Bhalla score was used to assess radiological severity of bronchiectasis, and the Bronchiectasis Severity Index (BSI) was used to assess the clinical severity. Blood and sputum samples were collected to assess blood cell count, erythrocyte sedimentation rate, c-reactive protein, immunological status (IgA, IgE, IgM, IgG, and IgG subclasses), and microbiological analysis.

Results: A total of 106 patients were enrolled in the study; 30.2% had concomitant asthma and were characterized by higher frequency of bronchiectasis exacerbation, despite higher Bhalla score and lower BSI compared to patients without asthma. *Pseudomonas aeruginosa* was more frequently isolated from the sputum of bronchiectasis patients without asthma. Total serum IgG, IgG1, and IgG3 were lower in patients with asthma. Blood eosinophils and exhaled nitric oxide were higher in patients with associated asthma. The presence of asthma and presence of *Pseudomonas* in sputum were the only significant determinants of frequent exacerbations in a binary logistic regression analysis.

Conclusion: The coexistence of asthma and bronchiectasis is associated with an independent increase in the risk of bronchiectasis exacerbation despite lower radiological and clinical severity indexes. Asthmatic airway inflammation could promote an enhanced “Cole’s Cycle” that is responsible for a higher frequency of exacerbations.

ARTICLE HISTORY

Received 13 July 2020
Revised 26 October 2020
Accepted 24 November 2020

KEYWORDS

Bronchiectasis; asthma; inflammation; exacerbation; comorbidities

Introduction

Once considered a neglected disease, non-cystic fibrosis bronchiectasis (NCFB) is a relatively rare and heterogeneous respiratory disorder affecting roughly 163 per 100,000 adults in Italy, with prevalence increasing to 11.1 cases per 100,000 person-years (1). It affects roughly 52.3 per 100,000 adults in the USA, with an increasing prevalence of 8% since 2001 (2). The growing prevalence of bronchiectasis is probably due to the extensive use of chest high-resolution computed tomography (HRCT), aging (1), and increasing interest from the scientific community.

Bronchiectasis is a chronic and irreversible respiratory disease characterized by abnormal dilatation of the bronchi, resulting in high sputum production, frequent exacerbations, impaired quality of life, and

declining lung function (3). Bronchiectasis greatly impacts welfare and healthcare systems similarly to COPD (4–7).

Although recent studies have tried to focus on the etiopathogenesis of the disease, only approximately 50% of patients have a clear cause of bronchiectasis, reflecting our poor knowledge of the disorder (8). Bronchial asthma is the sixth most common cause of bronchiectasis (ranging from 3% to 7%) (8), with a prevalence of 2.7–42% (9–11), but a clear mechanism has not been determined. Real-life data show that bronchiectasis is present in a wide range of patients with asthma (from 0.8% to 77%) (9–25), particularly those with severe phenotypes (12,13,22,26).

Though the coexistence of bronchiectasis and asthma has been reported in many studies, few studies

have investigated the relationship between bronchiectasis and asthma. In the latest international recommendations for asthma and COPD (27,28), bronchiectasis is defined as a "treatable trait" that should be investigated. This is particularly relevant in severe conditions or frequent exacerbations despite optimal therapy, because it could have a tremendous impact on disease progression at an individual level.

In addition, the combined presence of both diseases raises concerns about treatment; inhaled corticosteroids are fundamental for the treatment and management of bronchial asthma (28) but are not formally indicated for bronchiectasis (29) because they seem to promote and sustain bacterial load and exacerbations (30–33). Therefore, we investigated the clinical impact of asthma in bronchiectasis in terms of disease severity and the risk of exacerbations.

Methods

Study design

We prospectively collected data of patients affected by clinically relevant bronchiectasis, with or without a history of asthma or COPD, who attended our outpatient clinic at Respiratory Diseases and Pulmonary Rehabilitation—Policlinico Universitario di Catania (Catania, Italy) between March 2018 and June 2019. We included adult patients affected by radiologically significant bronchiectasis confirmed by HRCT. Patients affected by cystic fibrosis, primary ciliary dyskinesia (PCD), traction bronchiectasis, allergic bronchopulmonary aspergillosis (ABPA), α 1-antitrypsin deficiency, and significant immunodeficiency or unable to give consent were excluded.

The study followed the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and was approved by the local Ethic Committee (Comitato Etico Catania 1, num. protocol: CE 108/2018/PO). All enrolled patients provided written informed consent.

Clinical assessments

All patients performed clinical assessments while in a stable state. Smoking status and clinical respiratory and non-respiratory history were recorded, and lung function tests were performed in line with ATS/ERS guidelines (34). In patients with history of asthma or symptoms of episodic breathlessness, wheezing, cough, and chest tightness, asthma was confirmed or diagnosed according to the latest GINA recommendations (28). All the patients performed bronchial reversibility

test and asthma was confirmed with a gain in FEV1 of 12% and 200 ml from the pre-bronchodilator value.

Asthma symptom control was assessed by the Asthma Control Tests (ACT) (35). Blood and sputum samples were collected to assess markers of inflammation, including erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP), immunological status (IgA, IgE, IgM, IgG, and IgG subclasses), and microbiological analysis.

The presence of COPD was defined according to the medical history; previous or current smoke attitude and presence of emphysema on CT scan.

We recorded the number of exacerbations of bronchiectasis in the previous year, according to the British Thoracic Society guidelines (36) and the recent consensus on the definition of pulmonary exacerbation for clinical research (37). Pulmonary exacerbation was defined as a deterioration from baseline of three or more of the following symptoms: increased cough; change in sputum volume or consistency; increased sputum purulence; increased dyspnea or decreased exercise tolerance; the presence of fatigue or malaise; hemoptysis, and a clinically determined change in bronchiectasis treatment (fever $>38^{\circ}\text{C}$, wheezing, reduced pulmonary function, changes in chest sounds, radiographic changes consistent with a new infectious process).

Radiological assessment

All patients underwent HRCT scans to define the type, severity, and extension of bronchiectasis. In addition to the Neidich criteria for the diagnosis of bronchiectasis (38), the presence of bronchiectasis was confirmed using the following criteria: lack of tapering in the bronchi, dilation of the bronchi with a luminal diameter larger than that of the adjacent pulmonary artery, or the presence of peripheral bronchi within 1 cm of the costal pleural surface or the adjacent mediastinal pleural surface (39). The radiological severity of bronchiectasis was measured by the Bhalla score (40) based on the number of segments involved, the severity of wall thickening and bronchial dilatation, and the presence of mucus plug, emphysema, and consolidations. The maximum Bhalla score is 25 and is inversely related to radiological severity.

Clinical severity assessment

We measured the severity of bronchiectasis using the Bronchiectasis Severity Index (BSI) (41), a multidimensional scoring system with an excellent predictive

Table 1. Clinical and functional characteristic of bronchiectasis patients with and without associated asthma.

	All	Bronchiectasis with asthma <i>n</i> = 32	Bronchiectasis <i>n</i> = 74	<i>p</i> values
Age	60.7 ± 13.1	54.8 ± 8.9	63.4 ± 13.9	0.002
Females %	61.3	65.6	59.8	0.551
Current smokers %	11.3	6.3	14.1	0.281
Ex-smokers %	33	21.9	39.4	0.110
Atopy %	26.2	63.5	10.8	<0.001
COPD %	32.1	9.4	43.1	0.001
CRS %	31.1	42.9	10.6	0.003
GERD %	37.7	50.0	34.8	0.148
BMI	25 ± 5.7	25.9 ± 4.7	24.7 ± 6.1	0.335
Exacerbation rate	3.58 ± 1.9	4.78 ± 2.12	3.05 ± 1.60	<0.001
Bhalla score	15 ± 4.8	17.2 ± 3.1	14.1 ± 5.1	0.002
BSI	8.29 ± 4.9	6.41 ± 3.06	9.11 ± 5.32	0.008
Lobes involved	4.15 ± 1.6	4.26 ± 1.703	3.91 ± 1.510	0.309
<i>Pseudomonas</i> ^a (%)	22.6	7.7	37.3	0.005
FEV1 % predicted	81.9% ± 32.8	89.3 ± 27.9	78.7 ± 34.5	0.129
FVC % predicted	87.5 ± 27	92.0 ± 23.6	85.6 ± 29.3	0.275
FENO ppb	32 ± 25.5	43.0 ± 28.4	18.0 ± 11.2	0.001

Data are presented as mean ± SD or %, unless otherwise stated. COPD: Chronic Obstructive Pulmonary Disease; CRS: Chronic Rhino-Sinusitis; GERD: Gastro-Esophageal Reflux Disease; BMI: Body Mass Index; FEV1: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity; FeNO: Fractional exhaled Nitric Oxide. Data presented in bold type are statistically significant.

^aThe analysis was performed in 85 (21 patients were not able to expectorate).

index for exacerbations, hospital admissions, and mortality. The BSI score is influenced by age, body mass index (BMI), number of lobes involved by bronchiectasis, number of exacerbations in the previous year, bacterial colonization (especially *Pseudomonas aeruginosa*) and hospitalizations in the past 2 years. We calculated the BSI using the panel tools available online at www.bronchiectasis.eu (42).

Statistical analysis

Patient characteristics and continuous variables defined by the Kolmogorov-Smirnov test were expressed as mean and standard deviation (SD) or *n* (%). Differences between the two groups were tested by the Mann-Whitney test for non-normally distributed variables. For analysis of more than two groups, ANOVA was used for normally distributed variables. *P* < 0.05 was considered significant. Data were analyzed using SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA). Binary logistic regression was performed with exacerbation as a dependent variable against asthma, COPD, *Pseudomonas*, and age.

Results

A total of 106 patients were consecutively enrolled in the study; 74 patients had bronchiectasis without asthma and 32 patients had both bronchiectasis and asthma. The baseline characteristics of all patients and the two groups are reported in Table 1. The immunological status of the two groups is compared in Table 2. We found significant differences between the two groups in regards to age, number of exacerbations,

clinical and radiological severity of bronchiectasis (BSI and Bhalla score), and *P. aeruginosa* isolation (Table 1). Furthermore, eosinophil count and total IgG, IgG1, and IgG3 levels were significantly different between the two groups (Table 2).

Patients with only bronchiectasis had significantly more frequently COPD as a comorbidity compared to the bronchiectasis group with asthma. Also, 9.6% of patients with bronchiectasis and asthma showed emphysema on CT scan, had a smoking attitude (former or active) plus some clinical features suggestive of COPD. We found no significant differences between the two groups in terms of lung function and the number of lobes involved.

Binary logistic regression analysis of asthma, COPD, *Pseudomonas*, and age with frequent exacerbations (defined as three or more exacerbations in the previous year) (41) as the dependent variable showed that asthma and *Pseudomonas* were the only significant variables (6.339, *p* = 0.013 and 4.962, *p* = 0.014, respectively). Atopy and CRS were detected predominantly in the bronchiectasis group with asthma (Table 1).

Sputum samples were only collected only in 85 patients because 21 patients were not able to expectorate or the sample collected was inadequate. *P. aeruginosa* was more frequently isolated in bronchiectasis patients without asthma than patients with only bronchiectasis.

Discussion

Our main result is that asthma may impact bronchiectasis as an independent factor for exacerbation in

Table 2. Immunological features of bronchiectasis patients with and without associated asthma.

	Bronchiectasis with asthma <i>n</i> = 32	Bronchiectasis <i>n</i> = 74	<i>p</i> values
Blood eosinophils/mcl	478.1 ± 595.8	191.6 ± 186.8	0.001
CRP mg/L	5.46 ± 7.62	8.24 ± 11.75	0.269
ESR mm/h	24.4 ± 13.7	29.9 ± 20.4	0.202
Serum IgE IU/ml	318.2 ± 520.8	126.0 ± 189.0	0.055
Serum IgA	193.2 ± 80.8	267.1 ± 212.6	0.103
Serum IgM	135.6 ± 81.3	115.0 ± 59.8	0.199
Serum IgG	1039.5 ± 273.7	1215.5 ± 377.9	0.041
Serum IgG1	595.7 ± 180.7	794.5 ± 255.3	0.001
Serum IgG2	376.3 ± 183.5	412.5 ± 201.7	0.462
Serum IgG3	36.9 ± 20.5	58.1 ± 33.4	0.007
Serum IgG4	122.3 ± 106.1	82.8 ± 121.0	0.179

Data are presented as mean ± SD. ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; Ig: immunoglobulin; Data presented in bold type are statistically significant.

patients with concomitant bronchiectasis, which is in line with another recent study conducted by Mao (11). Patients with coexistent bronchiectasis and asthma present with less stable disease and symptom control (lower ACT), and they experience more exacerbations per year despite lower radiological and clinical severity (i.e. BSI). *P. aeruginosa* isolation from sputum samples is the main recognized independent risk factor for exacerbation and disease severity (29,41,43–45), and this was more common in patients without asthma in the present study. Other variables, such as gender, BMI, radiological extension (number of involved lobes), and functional tests, did not differ between the two groups, which is in contrast to previous findings (11).

Patients with bronchiectasis and concomitant asthma were younger and had a significant association with asthma-related features, such as atopy, chronic rhinosinusitis, blood eosinophil count, and fractional exhaled nitric oxide (FeNO) levels. In the present study, atopy was detected in 26.2% of all patients. In previous studies (9,46–49), the presence of atopy in bronchiectasis ranged from 25% to 48.8%. However, the role of atopy in bronchiectasis is not clear, as our results are also in line with the prevalence of atopy in the general population (50).

Another interesting result from this study is the higher blood eosinophil count in patients with bronchiectasis and asthma compared to bronchiectasis only. This result was not reported by Mao and may have relevant implications on treatment.

Bronchiectasis is a chronic, progressive, and irreversible respiratory disease sustained by chronic infection and progressive damage in which germs play a predominant role (50). Chronic inflammation is responsible for high sputum production, frequent exacerbations, impaired quality of life, and lung function decline. The concomitant presence of asthma and high level of eosinophils in bronchiectasis is suggestive of a type 2 endotype inflammation that could be

considered a treatable trait and a target for new biological anti-interleukin 5 (IL5) drugs, as already reported in a few clinical cases (51,52). The eosinophilic inflammation is responsible of glandular hypertrophy, mucus hypersecretion, and bronchial obstruction, especially in small airways (53). Furthermore, cationic eosinophil proteins (54), such as eosinophil peroxidase (EPO) (55), proteolytic enzymes (trypsin), and metalloproteases, directly damage the bronchial wall and lead to impaired mucociliary clearance, which is responsible for the mucoid impact (55,56) and more severe disease (57). Moreover, impairment of matrix metalloproteinases (MMPs) and tissue inhibitor of MMPs (TIMPs), resulting in degradation of the extracellular matrix, tissue destruction, and airway remodeling with loss of the physiological structure, has been demonstrated in both asthma and bronchiectasis (58).

Although bronchiectasis is classically considered to be sustained by neutrophilic inflammation, eosinophils are increasingly being recognized for roles in the disease (25,59–61), and they likely generate an “enhanced” Cole’s “vicious cycle hypothesis” (which has been proposed to be due to an environmental insult, in conjunction with genetic susceptibility or an immune defect in host defense, resulting in a chain of events leading to progressive bronchial wall destruction and dilatation). Unfortunately, to the best of our knowledge, no guidelines or studies suggest a specific therapeutic approach in this cohort of patients, though biological treatment could be a valid treatment option in select cases (24).

We also found a significant difference in IgG levels between the two groups, as patients with bronchiectasis and asthma had lower levels of IgG, especially IgG1 and IgG3, than patients with bronchiectasis only. This result was also reported by Mao (11), but it was not discussed and is suggestive of immunological impairment that could lead to higher susceptibility to infection. Previously, Luján et al. (20) reported similar

findings related to steroid treatment, which raises concerns about the feasible role of corticosteroid therapy in modulating or promoting exacerbations. Whether IgG alterations are directly promoted by steroid treatment or are an intrinsic characteristic of patients with bronchiectasis and asthma that could describe a novel phenotype, it is difficult to determine.

The main limitation of this study was that patients reported outcomes were not collected and therefore the psychological impact of the association between asthma and bronchiectasis was not assessed. Moreover, considering that therapeutic strategies for bronchiectasis are heterogeneous and not fully standardized, it is possible that our results may have been partially affected by this heterogeneity.

Conclusions

We report that the coexistence of asthma and bronchiectasis is associated with an independent increase in the risk of bronchiectasis exacerbation despite the presence of lower radiological and clinical severity. Our findings are suggestive of a new phenotype with type 2 inflammation that could promote an enhanced Cole's Cycle. Further studies are needed to confirm our results and to understand the role played by the immune system in this relationship.

Authors' contributions

Sebastian Ferri and Giulia Cacopardo contributed in collecting data. Sebastian Ferri contributed also in analyzing and interpreting data, and in writing the manuscript. Enrico Heffler, Claudia Crimi, and Nunzio Crimi contributed in the conceptualization of the study design, data analysis and interpretation. Raffaele Campisi, Giovanni Paoletti and Francesca Puggioni contributed in critically interpret the results and writing the manuscript.

Consent to participate

All enrolled patients signed an informed consent.

Ethics approval

Comitato Etico Catania 1—num. Protocol: CE 108/2018/PO.

Conflicts of interest

Enrico Heffler declares participation to advisory boards and personal fees from AstraZeneca, Sanofi, GSK, Novartis,

Circassia, Nestlè Purina, Boheringer Ingheleim, Valeas, outside the submitted work; Francesca Puggioni declares personal fees from Allergy therapeutics, Almirall, AstraZeneca, Chiesi, Glaxo Smith Kline, Guidotti, Menarini, Mundipharma, Novartis, Sanofi, Valeas. All the other Authors do not have conflict of interest to declare.

ORCID

Sebastian Ferri  <http://orcid.org/0000-0002-1831-9672>
 Claudia Crimi  <http://orcid.org/0000-0002-9088-5214>
 Raffaele Campisi  <http://orcid.org/0000-0001-9305-6748>
 Giovanni Paoletti  <http://orcid.org/0000-0003-3953-9225>
 Francesca Puggioni  <http://orcid.org/0000-0001-6638-5626>
 Nunzio Crimi  <http://orcid.org/0000-0002-8591-4535>
 Enrico Heffler  <http://orcid.org/0000-0002-0492-5663>

References

1. Aliberti S, Sotgiu G, Lapi F, Gramegna A, Cricelli C, Blasi F. Prevalence and incidence of bronchiectasis in Italy. *BMC Pulm Med*. 2020;20(1):15. doi:10.1186/s12890-020-1050-0.
2. Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots DR. Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. *Chest*. 2012;142(2):432–439. doi:10.1378/chest.11-2209.
3. Whitters D, Stockley R. Immunity and bacterial colonisation in bronchiectasis. *Thorax*. 2012;67(11):1006–1013. doi:10.1136/thoraxjnl-2011-200206.
4. Ringshausen FC, de Roux A, Pletz MW, Hämäläinen N, Welte T, Rademacher J. Bronchiectasis-associated hospitalizations in Germany, 2005–2011: a population-based study of disease burden and trends. *PLoS One*. 2013;8(8):e71109. doi:10.1371/journal.pone.0071109.
5. Weycker D, Edelsberg J, Oster G, et al. Prevalence and economic burden of bronchiectasis. *Clin Pulm Med*. 2005; 12:205–209.
6. Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations in the United States, 1993–2006. *Chest*. 2010;138(4):944–949. doi:10.1378/chest.10-0099.
7. Gursel G. Does coexistence with bronchiectasis influence intensive care unit outcome in patients with chronic obstructive pulmonary disease? *Heart Lung*. 2006;35(1):58–65. doi:10.1016/j.hrtlng.2005.04.003.
8. Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soyza A, Polverino E, Van de Kerkhove C, Rutherford R, Davison J, et al. Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. *Ann Am Thorac Soc*. 2015;12(12):1764–1770. doi:10.1513/AnnalsATS.201507-472OC.
9. Pang J, Chan HS, Sung JY. Prevalence of asthma, atopy, and bronchial hyperreactivity in bronchiectasis: a controlled study. *Thorax*. 1989;44(11):948–951. doi:10.1136/thx.44.11.948.

10. Oguzulgen IK, Kervan F, Ozis T, Turktas H. The impact of bronchiectasis in clinical presentation of asthma. *South Med J*. 2007;100(5):468–471. doi:10.1097/SMJ.0b013e31802fa16f.
11. Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. *Eur Respir J*. 2016;47(6):1680–1686. doi:10.1183/13993003.01862-2015.
12. Lynch DA, Newell JD, Tschomper BA, Cink TM, Newman LS, Bethel R. Uncomplicated asthma in adults: comparison of CT appearance of the lungs in asthmatic and healthy subjects. *Radiology*. 1993;188(3):829–833. doi:10.1148/radiology.188.3.8351357.
13. Paganin F, S  n  terre E, Chanez P, Daur  s JP, Bruel JM, Michel FB, Bousquet J. Computed tomography of the lungs in asthma: influence of disease severity and etiology. *Am J Respir Crit Care Med*. 1996;153(1):110–114. doi:10.1164/ajrccm.153.1.8542102.
14. Grenier P, Mourey-Gerosa I, Benali K, Brauner MW, Leung AN, Lenoir S, Cordeau MP, Mazoyer B. Abnormalities of the airways and lung parenchyma in asthmatics: CT observations in 50 patients and inter- and intraobserver variability. *Eur Radiol*. 1996;6(2):199–206. doi:10.1007/BF00181147.
15. Park JW, Hong YK, Kim CW, Kim DK, Choe KO, Hong CS. High-resolution computed tomography in patients with bronchial asthma: correlation with clinical features, pulmonary functions and bronchial hyperresponsiveness. *J Investig Allergol Clin Immunol*. 1997;7(3):186–192.
16. Cukier A, Stelmach R, Kavakama JI, Terra Filho M, Vargas F. Persistent asthma in adults: comparison of high resolution computed tomography of the lungs after one year of follow-up. *Rev Hosp Clin Fac Med Sao Paulo*. 2001;56(3):63–68. doi:10.1590/s0041-87812001000300001.
17. Gupta S, Siddiqui S, Haldar P, Raj JV, Entwisle JJ, Wardlaw AJ, Bradding P, Pavord ID, Green RH, Brightling CE, et al. Qualitative analysis of high-resolution CT scans in severe asthma. *Chest*. 2009;136(6):1521–1528. doi:10.1378/chest.09-0174.
18. Bisaccioni C, Aun MV, Cajuela E, Kalil J, Agondi RC, Giavina-Bianchi P. Comorbidities in severe asthma: frequency of rhinitis, nasal polyposis, gastroesophageal reflux disease, vocal cord dysfunction and bronchiectasis. *Clinics (Sao Paulo)*. 2009;64(8):769–773. doi:10.1590/S1807-59322009000800010.
19. Menzies D, Holmes L, McCumesky G, Prys-Picard C, Niven R. Aspergillus sensitization is associated with airflow limitation and bronchiectasis in severe asthma. *Allergy*. 2011;66(5):679–685. doi:10.1111/j.1398-9995.2010.02542.x.
20. Luj  n M, Gallardo X, Amengual MJ, Bosque M, Mirapeix RM, Domingo C. Prevalence of bronchiectasis in asthma according to oral steroid requirement: influence of immunoglobulin levels. *Biomed Res Int*. 2013;2013:1–7. doi:10.1155/2013/109219.
21. 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(10):1246–1252. doi:10.1111/cea.12971.
22. Dimakou K, Gousiou A, Toubis M, Kaponi M, Chrysikos S, Thanos L, Triantafillidou C. Investigation of bronchiectasis in severe uncontrolled asthma. *Clin Respir J*. 2018;12(3):1212–1218. doi:10.1111/crj.12653.
23. Coman I, Pola-Bibi  n B, Barranco P, Vila-Nadal G, Dominguez-Ortega J, Romero D, Villasante C, Quirce S. Bronchiectasis in severe asthma: clinical features and outcomes. *Ann Allergy Asthma Immunol*. 2018;120(4):409–413. doi:10.1016/j.anai.2018.02.016.
24. Padilla-Galo A, Oliveira C, Fern  ndez de Rota-Garcia L, Marco-Galve I, Plata AJ, Alvarez A, Rivas-Ruiz F, Carmona-Oliveira A, Cebrian-Gallardo JJ, Mart  nez-Garcia MA, et al. Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: a study in 398 patients. *Respir Res*. 2018;19(1):43. doi:10.1186/s12931-018-0746-7.
25. Crimi C, Ferri S, Campisi R, Crimi N. The link between asthma and bronchiectasis: state of the art. *Respiration*. 2020;99(6):463–476. doi:10.1159/000507228.
26. Crimi C, Ferri S, Crimi N. Bronchiectasis and asthma: a dangerous liaison? *Curr Opin Allergy Clin Immunol*. 2019;19(1):46–52. doi:10.1097/ACI.0000000000000492.
27. Goldcopd.org. Available from: <https://goldcopd.org/> [last accessed 1 July 2020].
28. Ginasthma.org. Available from: <https://ginasthma.org/> [last accessed 1 July 2020].
29. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cant  n R, Torres A, Dimakou K, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50(3):1700629. doi:10.1183/13993003.00629-2017.
30. Garcha DS, Thurston SJ, Patel ARC, Mackay AJ, Goldring JJP, Donaldson GC, McHugh TD, Wedzicha JA. Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax*. 2012;67(12):1075–1080. doi:10.1136/thoraxjnl-2012-201924.
31. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;(3):CD010115. doi:10.1002/14651858.CD010115.pub2.
32. Festic E, Scanlon PD. Incident pneumonia and mortality in patients with chronic obstructive pulmonary disease. A double effect of inhaled corticosteroids? *Am J Respir Crit Care Med*. 2015;191(2):141–148. doi:10.1164/rccm.201409-1654PP.
33. Henkle E, Curtis JR, Chen L, Chan B, Aksamit TR, Daley CL, Griffith DE, Winthrop KL. Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis. *Eur Respir J*. 2019;54(1):1801896. doi:10.1183/13993003.01896-2018.
34. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805.
35. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: a survey for

- assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65. doi:10.1016/j.jaci.2003.09.008.
36. Pasteur MC, Bilton D, Hill AT, British thoracic society bronchiectasis non-CF guideline group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax*. 2010;65(Suppl 1):i1–i58. doi:10.1136/thx.2010.136119.
37. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, Chalmers JD, De Soyza A, Dimakou K, Elborn JS, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J*. 2017;49(6):1700051. doi:10.1183/13993003.00051-2017.
38. Naidich DP, McCauley DI, Khouri NF, Stitik FP, Siegelman SS. Computed tomography of bronchiectasis. *J Comput Assist Tomogr*. 1982;6(3):437–444. doi:10.1097/00004728-198206000-00001.
39. Martínez-García M-A, de la Rosa Carrillo D, Soler-Cataluña J-J, Donat-Sanz Y, Serra PC, Lerma MA, Ballestín J, Sánchez IV, Selma Ferrer MJ, Dalfo AR, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(8):823–831. doi:10.1164/rccm.201208-1518OC.
40. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, Naidich DP. Cystic fibrosis: scoring system with thin-section CT. *Radiology*. 1991;179(3):783–788. doi:10.1148/radiology.179.3.2027992.
41. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, Poppelwell L, Salih W, Pesci A, Dupont LJ, et al. The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med*. 2014;189(5):576–585. doi:10.1164/rccm.201309-1575OC.
42. EMBARC. Available from: <https://www.bronchiectasis.eu/severity-assessment> [last accessed 1 July 2020].
43. Evans SA, Turner SM, Bosch BJ, Hardy CC, Woodhead MA. Lung function in bronchiectasis: the influence of *Pseudomonas aeruginosa*. *Eur Respir J*. 1996;9(8):1601–1604. doi:10.1183/09031936.96.09081601.
44. Davies G, Wells AU, Doffman S, Watanabe S, Wilson R. The effect of *Pseudomonas aeruginosa* on pulmonary function in patients with bronchiectasis. *Eur Respir J*. 2006;28(5):974–979. doi:10.1183/09031936.06.00074605.
45. Chawla K, Vishwanath S, Manu MK, Lazer B. Influence of *pseudomonas aeruginosa* on exacerbation in patients with bronchiectasis. *J Glob Infect Dis*. 2015;7(1):18–22. doi:10.4103/0974-777X.150885.
46. Murphy MB, Reen DJ, Fitzgerald MX. Atopy, immunological changes, and respiratory function in bronchiectasis. *Thorax*. 1984;39(3):179–184. doi:10.1136/thx.39.3.179.
47. Varpela E, Laitinen LA, Keskinen H, Korhola O. Asthma, allergy and bronchial hyper-reactivity to histamine in patients with bronchiectasis. *Clin Allergy*. 1978;8(3):273–280. doi:10.1111/j.1365-2222.1978.tb03224.x.
48. Niksarlioğlu EY, Işık R, Uysal MA, Ünal D, Çamsarı G. Prevalence of atopy and allergic rhinitis in patients with adult non-cystic fibrosis bronchiectasis. *Turk J Med Sci*. 2019;49(2):551–557. doi:10.3906/sag-1807-229.
49. Säynäjäkangas O, Keistinen T, Tuuponen T, Kivelä SL. Links between hospital diagnoses of bronchiectasis and asthma. *Allergy*. 1997;52(11):1120–1122. doi:10.1111/j.1398-9995.1997.tb00186.x.
50. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med*. 2015;372(5):456–463. doi:10.1056/NEJMcp1412282.
51. Cole PJ. Inflammation: a two-edged sword—the model of bronchiectasis. *Eur J Respir Dis Suppl*. 1986;147:6–15.
52. Carpagnano GE, Scioscia G, Lacedonia D, Curradi G, Foschino Barbaro MP. Severe uncontrolled asthma with bronchiectasis: a pilot study of an emerging phenotype that responds to mepolizumab. *JAA*. 2019;12:83–90. doi:10.2147/JAA.S196200.
53. Rademacher J, Konwert S, Fuge J, Dettmer S, Welte T, Ringshausen FC. Anti-IL5 and anti-IL5R α therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series. *Eur Respir J*. 2020;55(1):1901333. doi:10.1183/13993003.01333-2019.
54. Mauad T, Silva LFF, Santos MA, Grinberg L, Bernardi FDC, Martins MA, Saldiva PHN, Dolnikoff M. Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. *Am J Respir Crit Care Med*. 2004;170(8):857–862. doi:10.1164/rccm.200403-305OC.
55. Frigas E, Gleich GJ. The eosinophil and the pathophysiology of asthma. *J Allergy Clin Immunol*. 1986;77(4):527–537. doi:10.1016/0091-6749(86)90341-6.
56. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, Raymond WW, Lachowicz-Scroggins ME, Di Maio S, Hoffman EA, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest*. 2018;128(3):997–1009. doi:10.1172/JCI95693.
57. Takemura M, Niimi A, Minakuchi M, Matsumoto H, Ueda T, Chin K, Mishima M. Bronchial dilatation in asthma: relation to clinical and sputum indices. *Chest*. 2004;125(4):1352–1358. doi:10.1378/chest.125.4.1352.
58. Bumbacea D, Campbell D, Nguyen L, Carr D, Barnes PJ, Robinson D, Chung KF. Parameters associated with persistent airflow obstruction in chronic severe asthma. *Eur Respir J*. 2004;24(1):122–128. doi:10.1183/09031936.04.00077803.
59. Polverino E, Rosales-Mayor E, Dale GE, Dembowski K, Torres A. The role of neutrophil elastase inhibitors in lung diseases. *Chest*. 2017;152(2):249–262. doi:10.1016/j.chest.2017.03.056.
60. Tsikrika S, Dimakou K, Papaioannou AI, Hillas G, Thanos L, Kostikas K, Loukides S, Papiris S, Koulouris N, Bakakos P, et al. The role of non-invasive modalities for assessing inflammation in patients with non-cystic fibrosis bronchiectasis. *Cytokine*. 2017;99:281–286. doi:10.1016/j.cyto.2017.08.005.
61. Chalmers JD, Chotirmall SH. Bronchiectasis: new therapies and new perspectives. *Lancet Respir Med*. 2018;6(9):715–726. doi:10.1016/S2213-2600(18)30053-5.