Respiration

Clinical Investigations

Respiration 2020;99:463–476
DOI: 10.1159/000507228

Received: November 4, 2019
Accepted after revision: March 9, 2020
Published online: May 28, 2020

The Link between Asthma and Bronchiectasis: State of the Art

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Keywords
Asthma · Bronchiectasis · Comorbidities in asthma · Airways disease

Abstract
The nonrecognition of asthma-associated comorbidities is often responsible for the therapeutic failure and the worsening of symptoms, and it is associated with frequent exacerbations, higher disease severity, and increased health costs. Bronchiectasis, one of the most frequent asthma-associated comorbidities, can increase airways inflammation and exacerbation rates and cause respiratory functional impairment. The aim of this article is to review the interactions between bronchiectasis and asthma, in order to better identify patients in the overlap between the 2 diseases and to select an "ad hoc" therapy. A literature search on PubMed/MEDLINE was performed using the following search terms: bronchiectasis in asthma, the association between asthma and bronchiectasis, comorbidities in asthma, and severe asthma. This review analyzed the following items: incorrect or underestimated diagnosis of asthma and bronchiectasis, prevalence of bronchiectasis in asthma, the impact of bronchiectasis in asthma, radiological imaging features of the 2 diseases, etiopathogenesis, and common causes (such as gastroesophageal reflux disease, immune deficits, chronic rhinosinusitis and allergic bronchopulmonary aspergillosis, and treatment of asthma and bronchiectasis). The concomitant presence of bronchiectasis and asthma should be suspected and investigated in patients with severe asthma, frequent exacerbations, and not responding to standard therapy. This clinical phenotype, characterized by a more severe disease, worse outcomes, and functional decline, must be readily recognized in order to choose the most appropriate therapeutic approach, able to potentially improve the management of bronchial asthma, to prevent the onset of exacerbations as well the functional decline, and to reduce health costs.

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Introduction

The recently published document Global INitiative for Asthma 2019 [1] underlined that the primary objective for the achievement of the control of asthmatic patients is identification and management of comorbidities other than verifying the adherence to the therapy. The nonrecognition of the several asthma-associated comorbidities is often responsible of the therapeutic failure and the worsening of symptoms, associated with frequent exacer-

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bations, a higher disease severity, and increased health costs [2, 3]. Among the more and more frequent asthma-associated comorbidities [4], bronchiectasis represents a heterogeneous and often unrecognized disease, which makes the management and therapeutic success of asthma more difficult and complex [5]. The increase of mean age, survival, chronic diseases such as chronic obstructive pulmonary disease (COPD) and asthma, and the higher use of high-resolution computer tomography (HRCT) made it possible to detect more frequently the presence of bronchiectasis [6]. Several studies [7–20] showed that the concomitant presence of bronchiectasis and asthma in the same patient could increase airways inflammation and exacerbations rates and cause a functional decline. Severe asthma seems to be associated with a high rate of bronchiectasis. The management of the single diseases is widely supported by international Guidelines [1, 21, 22], but few studies to date assessed their association or how the 2 diseases affect each other [23–25]. The more and more frequent presence of bronchiectasis in patients affected by bronchial asthma, especially in severe forms, made it seems that asthma could have a causative role in the development of bronchiectasis, where mucus, infection, and chronic inflammation represent the common "treatable traits" [26–28], which have to be considered by pneumologists for a correct therapeutic approach. The several phenotypes of asthma [29] need a different therapeutic approach characterized by an adequate and individualized therapeutic plan (precision therapy) [30–32]. It is therefore essential to understand how much and in what way bronchiectasis interact with asthma, in order to identify patients in overlap between the 2 diseases and to select an "ad hoc" therapy.

Methods

A literature search on PubMed/MEDLINE was performed using the following search terms: bronchiectasis in asthma, association between asthma and bronchiectasis, comorbidities in asthma, severe asthma, without time limits.

Asthma and Bronchiectasis: Incorrect or Underestimated Diagnoses

The prevalence of asthma, one of the more common and heterogeneous respiratory diseases, is progressively increasing [33], and approximately 5–10% [34, 35] of patients are affected by severe (defined as the need to high-dose inhaled corticosteroids associated with a second controller and/or systemic steroids for the disease control) [1, 36, 37] and treatment-resistant forms. Under the "umbrella" of heterogeneous forms of asthma [38], there are also allergic, hypereosinophilic and noneosinophilic, and steroid-resistant forms (defined as "neutrophilic asthma") [39–41]. About 20–30% of asthmatic patients are affected by this form, characterized by an intense neutrophilic inflammation at bronchial level [42] such as in bronchiectasis.

Among the most frequent comorbidities of asthma, bronchiectasis represents a very heterogeneous disease with a negative impact on its severity, pathophysiology, evolution, and prognosis.

Bronchiectasis is relatively uncommon, with an estimated prevalence of about 139 cases/100,000 US adults [43], especially women, even if Seitz et al. [44] reported a significant increase of the prevalence during the last years, with an annual incremental rate of 8% starting from 2001.

Albeit different, these 2 diseases share similar functional and clinical features which, in practice, can lead to a misdiagnosis in favor of asthma and an underestimation of bronchiectasis. In fact, the gold standard tool for the diagnosis of bronchiectasis is chest HRCT [45], which is not routinely indicated for asthmatic patients and usually performed in selected and complex cases only. On the contrary, the diagnosis of asthma is mainly based on functional criteria such as reversibility of airway obstruction and hyperreactivity tests [1], according to the American Thoracic Society/European Respiratory Society Guidelines [46]. However, these tests have high susceptibility but low specificity, due to the fact that reversibility of airway obstruction can be also observed in other diseases such as COPD and bronchiectasis [47–51], with a variability ranging from 5 to 25% [52]: this can lead to a misdiagnosis and a treatment delay if these tests are not associated with patients' clinical status. In any case, the reversibility observed in bronchiectasis patients was related to the presence of a chronic eosinophilic inflammation [53]. The bronchial hyperreactivity test is positive in several systemic and respiratory diseases [54, 55] and in 50% of patients with bronchiectasis [56], especially in case of concomitant hypereosinophilia [53]. Considering the clinical features of both asthma and bronchiectasis, the presence of dyspnea, wheezing, cough, and mucus production are common overlapping symptoms of the 2 diseases [57], even if of patients' age, duration of asthma, the frequency of exacerbations, and infections with mucus purulence are key features to suspect the presence of bronchiectasis.

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Table 1. Main features of asthma and bronchiectasis

	Asthma	Neutrophilic asthma	Bronchiectasis [53]	Eosinophilic bronchiectasis [53]
Obstruction	Present	Present	Often present [50]	Often present
Reversibility	Present	Not always present	Not always present	Present [48]
Inflammation	Mainly eosinophilic	Mainly neutrophilic	Prevalentemente Neutrophilic	Mainly eosinophilic
FeNO	High	Not always high	Nor always high	High
Onset	Early onset	Late onset	Early onset	Late onset
Severity	Variable	Severe	Variable	Severe
Allergy	Often present	Not always present	Not always present	Not always present
Exacerbations	Variable	Frequent and severe	Variable	Frequent and severe
IL-8	Low	High	High	Low
Response to ICS	Present/good	Poor	Poor	Present

FeNO, exhaled nitric oxide; ICS, inhaled corticosteroids; IL, interleukin.

Sputum

The eosinophilic inflammation, observed in 31% of bronchiectasis patients [53], can create further confusion because, as stated before, it can result in clinical/functional phenotypes similar to typical asthma. The differential cytologic examination of sputum [58, 59] can represent a valid noninvasive tool for identifying the features of a chronic inflammation; however, this method, even if validated and to date widely used [60], has some limitations, such as operator- and center-dependent sample collection and analysis. The "induced sputum" can give different results based on the method used for the sputum induction, the collection timing, and clinical status of the patient.

As recently reported by Dimakou et al. [18] and Padilla et al. [20], productive cough with mucopurulent sputum, often positive for potential pathogen microorganisms such as *Haemophilus influenzae* and *Pseudomonas aeruginosa* (this latter widely considered an independent factor for mortality and worse outcomes in bronchiectasis) is often present in patients with asthma/bronchiectasis [61], these symptoms are highly indicative of the concomitant presence of asthma and bronchiectasis.

Nitric Oxide

Exhaled nitric oxide (FeNO), an important diagnostic parameter for the evaluation of the upper airways' inflammation, is used in the clinical practice for evaluating the asthmatic disease [62]. It is recently also been considered for the evaluation of the inflammatory status in patients with bronchiectasis; in fact, a study published in 2018 [20] showed that these patients, especially in presence of eosinophilic inflammation, have higher levels of FeNO and a higher reversibility to the bronchodilator test respect to bronchiectasis patients with a prevalent neutrophilic inflammation (lower levels of FeNO and poor reversibility). Several trials showed that FeNO levels in asthmatic patients are related with the upper airways' inflammation, the bronchial reactivity, the disease severity, and the presence of eosinophilia [63–69]. On the contrary, the role of FeNO in patients with bronchiectasis is debated; in fact, some studies showed that FeNO levels are related to the severity of bronchiectasis [70], thus others showed that FeNO levels are low and in particular lower than those observed in asthmatic patients [20]. A recently published study [53] tried to clarify this problem, emphasizing that FeNO and interleukin-13 (IL-13) levels and reversibility to bronchodilation are higher in patients with bronchiectasis and concomitant eosinophilic inflammation (or a mixed eosinophilic-neutrophilic inflammation), as observed in asthmatic patients. It is therefore conceivable that FeNO is a valid parameter for identifying asthmatic patients and bronchiectasis patients (lower FeNO levels compared to asthmatic patients only) and bronchiectasis patients with similar asthmatic symptoms (higher FeNO levels compared to bronchiectasis patients only). The cut-off value commonly used for identifying patients with asthma/bronchiectasis from nonasthmatic patients is 22.5 ppb [71].

Finally, it is possible to identify 4 phenotypes (2 for asthma and 2 for bronchiectasis) with neutrophilic or eosinophilic inflammation, which can have common characteristics and an impact on the correct diagnosis, as summarized in Table 1.

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Table 2. Prevalence of bronchiectasis in asthma

Study, year	Patients	Primary objective	Frequency of BE	Factors associated to BE	Type of BE
Lynch et al. [7], 1993	48	Radiological signs in asthma	77%	NR	Cylindrical
Paganin et al. [8], 1996	126	Radiological signs in asthma	20–80%	Not allergic asthma, severity	20–80% cylindrical 60% varicose
Grenier et al. [9], 1996	50+10	Radiological signs in asthma	28.5%	Disease severity	20% cylindrical 10% cystic
Park et al. [10], 1997	57	Clinical status	17.5%	Disease severity, duration of disease and obstruction	NR
Cukier et al. [11], 2001	14	Follow-up HRCT in asthma	36% 1° HRCT versus 21% 2° HRCT	Clinical instability	80% cylindrical 20% cystic
Oguzulgen et al. [12], 2007	1,680	Characteristics of asthma/BE patients	3%	Disease severity, hospitalizations	NR
Gupta et al. [13], 2009	467	Radiological signs in asthma	40%	Duration of the disease, FEV1/FVC <75%	NR
Bisaccioni et al. [14], 2009	105	Comorbidities in asthma	24.8%	NR	NR
Kurt et al. [74], 2009	46	Radiological signs in mold to moderate asthma, 6 years follow-up	13/15.2%	NR	85% cylindrical 15% cystic
Menzies et al. [15], 2011	133	Radiological signs in asthma associated to ABPA	35.3%	Bronchial obstruction, *Aspergillus fumigatus*	NR
Luján et al. [16], 2013	100 (50 SD and 50 NSD)	BE related to steroids use	20% SD versus 4% NSD	Age, duration of the disease, worse bronchial obstruction and steroids use	NR
Weatherburn et al. [17], 2017	84.505 +1.339.873	Prevalence of comorbidities	0.8%	NR	NR
Dimakou et al. [18], 2018	40	BE in severe asthma	67.5%	Antibiotics use, sputum, bacterial colonization	85% cylindrical 10% varicose 10% cystic
Coman et al. [19], 2018	184	Characteristics of asthma with BE	47%	Exacerbations, eosinophily, GERD, mild atopy	NR
Padilla-Galo [20], 2018	398	Characteristics of asthma with BE	28.4% (20.6% moderate asthma and 33.6% severe asthma)	Sputum, disease severity, low levels of FeNO	92.2% cylindrical and 7.1% cystic
Kim et al. [75], 2018	91	Radiological signs in severe asthma	35.2%	Disease severity, age, worse FEV1, female sex	NR
Heffler et al. [76], 2019	437	Comorbidities in severe asthma	16%	Disease severity, exacerbations, hospitalizations, > eosinophils and IgE	NR
Garcìa-Clemente et al. [77], 2019	108	Prevalence of BE in asthma	35%	Age, duration of the disease, disease severity, hospitalizations, flow obstruction	NR
Xie et al. [78], 2019	2,207	Prevalence of BE in asthma	19.7%	Haemoptysis, exacerbations, productive cough, hospitalizations	87% cylindrical and 13% varicose

ABPA, allergic bronchopulmonary aspergillosis; BE, bronchiectasis; FeNO, exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high resolution computed tomography; GERD, gastroesophageal reflux disease; IgE, immunoglobulin E; NR, not reported; NSD, non-steroid-dependent; SD, steroid-dependent.

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Table 3. Characteristics of patients with asthma and bronchiectasis

General characteristics
Advanced age
Longer duration of asthma
Clinical characteristics
Increased daily sputum
Higher number of exacerbations
Worse severity of asthma
Not always allergy/atopy
Functional characteristics
Worse obstruction to air flow (FEV1/FVC and FEV1%)
Reversibility not always present
Higher functional impairment during time
Microbiological characteristics
Generally mucopurulent sputum
Inscreased prevalence of PPMs
Higher prevalence of *Pseudomonas aeruginosa*, *Haemophilus influenzae* and fungi
Treatment characteristics
Poor response to ICS
Better response to antibiotics
Good response to macrolides (acute and chronic treatment)
Increased need of systemic steroids
Mucolytics can work
Inflammatory markers
Mainly neutrophilic inflammation
Lower levels of FeNO respect to asthma population
Higher levels of FeNO respect to healthy population
Prognostic factors
Increased mortality
Increased exacerbations risk
Increased hospitalisation risk
Asthma unresponsive to the actual steroid therapy

FeNO, exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; PPMs, potential pathogen microorganisms.

Prevalence of Bronchiectasis in Asthma

Apart idiopathic forms (50%), the most common causes of bronchiectasis are infections (20%), COPD (5–15%), connective tissue diseases (8–10%), immunodeficiencies (5–6%), and asthma (3–7%) [50, 72].

Bronchiectasis can be identified before the definitive diagnosis of asthma [73] or during the disease course, with a wide frequency ranging from 0.8 to 77% [7–20] (17.5–40% [10, 15, 74] in mild forms and 67.5–77% [7, 18] in severe forms [Table 2]). This wide variability is caused by the different analytical methods used in each study: type of enrolled patient populations, sample size, diagnostic criteria for the detection of bronchiectasis (e.g., the CT scan is often operator dependent), and not known causes of diagnosed bronchiectasis. In addition, the characteristics of the asthmatic population are also different between studies in terms of asthma severity and phenotype; studies evaluating bronchiectasis in asthma showed that chest HRCT is often performed in patients with clinical features already indicative for bronchiectasis: this is a bias for the detection of the real prevalence of bronchiectasis.

Finally, bronchiectasis seems to be more frequent in patients with severe asthma, as demonstrated by the study of Paganin et al. [8] on asthmatic patients stratified according the disease severity: bronchiectasis is present in 50–60% of patients with severe asthma respect to 20% of patients with mild asthma.

Impact of Bronchiectasis in Asthma

The role of bronchiectasis in the natural evolution of bronchial asthma is not yet fully understood, but several trials have already demonstrated the possible association with a worsening of clinical and functional outcomes of asthma [75], a higher bronchial obstruction (low forced expiratory volume in 1 s – FEV1), and a higher reversibility in case of eosinophils [10, 13, 15]. Similarly, it is not clear how the presence of asthma in bronchiectasis patients, compared to other causes of bronchiectasis, can influence the course of the disease [79]. Bronchiectasis and asthma are more frequently observed in older patients, in patients with severe asthma and a longer duration of the disease, and in forms poorly responsive to the current standard therapy. Patients can benefit from a treatment with mucolytics, in order to improve the mucus management, and antibiotics, due to the already mentioned presence of productive cough and mucopurulent sputum, often positive for potential pathogen microorganisms such as *Haemophilus influenzae* and *P. aeruginosa* [18, 20].

The simultaneous presence of asthma and bronchiectasis, moreover, is associated with a greater risk of exacerbations of the single diseases, as shown by Coman et al. [19] and Mao et al. [80]. It is still unknown if the presence of bronchiectasis in asthma can have an impact on the clinical outcomes and the natural course of the disease.

The combination asthma and bronchiectasis can identify a population with not well-defined characteristics, as reported in Table 3.

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Imaging

The presence of bronchiectasis is highly probable in older patients with a long-term disease, a functional decline, and frequent exacerbations, especially if associated with bacterial infections caused by *P. aeruginosa*: in this case, a HRCT can be useful for confirming the diagnosis. A valid tool for identifying bronchiectasis is the NOPES score [20] (FeNO, Pneumonia, Exacerbations and Severity), which consider the FeNO value (cut-off 20.5 ppb), the disease severity and the number of exacerbations/pneumonia; the score ranges from 0 (low risk) to 4 (high risk).

Depending on using a score or relying on clinical suspicion, chest HRCT of patients with bronchiectasis can also show structural damages other than bronchiectasis. In fact, the airways remodeling is commonly observed in asthma, and it is characterized by radiological signs such as thickening of the bronchial wall [81–84], bronchial dilations [85], mucus plug, and air trapping. Several studies supported by the Severe Asthma Research Program showed that these radiological signs are associated with a more severe disease [81–83, 86–92], until to real clinical – radiological clusters [93]. Despite some literature correlating radiological imaging and asthma, at the time being few clinical trials showed a relationship between bronchiectasis and disease severity. Using elective radio-diagnostic tools, such as HRCT, a gold standard for the diagnosis, it is possible to detect the presence of bronchiectasis, even if this method is not routinely used in the diagnostic algorithm of bronchial asthma. Over the years, different systems of classification and radiological evaluation of bronchiectasis have been used [94–97]. Actually, the Naidich et al. [95] criteria, which are able to evaluate the presence of bronchiectasis through both direct (such as the enlargement of the major bronchial diameter of the adjacent arterial vessel, the view of peripheral bronchi up to 1 cm away from the costal pleura, the lack of reduction of the bronchial lumen) and indirect (a thickening of the peribronchial wall, a mucus plugging, the tree-in-bud sign, a mosaic pattern, centrolobular nodules, air trapping, and atelectasis) signs, are the most used in the clinical practice. To date, no study has related the bronchiectasis severity and the asthma severity through the clinical – radiological scores, such as the Bhalla et al. [96] score or clinical scores such as the bronchiectasis severity index [98]. A study performed on 123 Chinese patients with bronchial asthma showed the HRCT can detect at least one structural damage, such as the thickening of the wall (57.7% of cases), bronchial dilations and bronchiectasis (51.2% of cases), and mucus plugging (22% of cases) [89]. Cylindrical bronchiectasis is more frequently observed at proximal level, while varicose and cystic bronchiectasis have predominantly a distal distribution [9]. Another large study performed on asthmatic patients stratified according the type (allergic vs. nonallergic) and the severity of the disease, highlighted that 60% of patients with severe asthma had varicose bronchiectasis; on the contrary, cylindrical bronchiectasis were observed in 20% of cases with mild asthma and in 50% of cases with severe allergic bronchial asthma [8].

Last but not least, the difference between bronchial dilation and bronchiectasis should be considered for a correct interpretation of chest HRCT performed on asthmatic patients [85]. The need of an appropriate distinction between bronchial dilation and bronchiectasis has been already mentioned in 1993 by Lynch et al. [7]; in particular, a clinical study performed in 2001 [11], where asthmatic patients were annually monitored with HRCT, showed that some baseline bronchiectasis were no more visible after 1 year. Therefore, in this case, it is more appropriate to define them as bronchial dilations rather than bronchiectasis, since the latter are irreversible by definition. The diagnosis of bronchiectasis in asthmatic patients should be performed with caution, taking always into account that bronchial asthma, especially if clinically unstable, can present often reversible bronchial dilations, which must be distinguished from bronchiectasis, although sharing similar radiological characteristics.

Etiopathogenesis

Bronchiectasis are present in all ages groups and can be idiopathic (43–50%) or secondary to other disease; these latter forms are certainly increased during the last decades due to the higher number of respiratory chronic comorbidities and systemic diseases such as rheumatoid arthritis and immune deficits, where bronchial asthma represents the fifth cause [72].

Until now, all the studies always considered these 2 diseases as an association between 2 distinct pathological processes, not considering a direct causal link between the 2 diseases. We believe that, while maintaining their individuality, asthma and bronchiectasis share some common aspects such as chronic inflammation, hypersecretion of mucus, oxidative stress, and airways remodeling (Fig. 1). Due to these similarities, it is possible to hypothesize a causal link between these 2 diseases, as they

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ASTHMA		BRONCHIECTASIS
Abnormal alveolar attachments Decreased elastic fibre content Changes in ECM composition Smooth muscle shortening	**LUNG REMODELING/DAMAGE**	Bronchial dilation Hypertrophy of muciparous glands
Inflammatory infiltrate (eosinophils, mast cells, lymphocytes and neutrophils)	**AIRWAY INFLAMMATION**	Airway inflammation (neutrophils)
Accumulation of mucus in lumen	**MUCUS PLUG**	Impaired mucociliary clearance
Airway wall thickening Muscle hyperreactivity	**AIRWAY OBSTRUCTION**	Sputum hypersecretion
INEFFECTIVE PULMONARY DEFENSE		

Fig. 1. A comparison between etiopathogenetic characteristics of asthma and bronchiectasis: highlights of shared features.

share superimposable although different "vicious circles," where the main protagonists are mucus and inflammation [24].

Mucus has a central role in these "vicious circles," because both asthma and bronchiectasis are considered hypersecretive diseases [99–103]. Bronchial secretions, an impaired mucociliary clearance and the airflow obstruction, can contribute to worse symptoms and to increase mortality [86–92, 104]. Mucus of patients with bronchial asthma is more viscous than that of patients with bronchiectasis, probably due to a defect of assembling of *mucina* molecules [105–108], even if the real etiopathogenetic mechanism is still unknown. These characteristics of the mucus, together with the epithelial fragility associated with the loss of hair cells, a significant hyperplasia of the caliciform glandular cells, the chronic and mainly eosinophilic inflammation (observed in 58% of cases) [92] compromise the mucociliary clearance and cause a thickening of the bronchial wall and airflow obstruction [81, 83]. The chronic inflammation observed in severe bronchial asthma, in particular the eosinophilic inflammation, is responsible of glandular hypertrophy with mucus hypersecretion, which is one of the essential elements of bronchial obstruction, especially at small airways level (as shown by autoptic results obtained from patients who died for asthma) [109]. The damage of the bronchial wall, characterized by cilia and bronchial epithelium destruction also induced by some cationic proteins of eosinophils [110] such as eosinophil peroxidase [92], proteolytic enzymes (trypsin), and metalloproteases, can justify the impaired mucociliary clearance and a more labile, brittle, and less resistant to mechanical triggers bronchial wall, which is in turn responsible for the mucoid impact [85, 92] associated with a more severe disease [84]. Mucous plugs of the bronchial tree represent a common characteristic of asthma, especially in severe forms, even in cases without bronchiectasis; the mucus viscosity, together with spasms of bronchial muscles, can be cause the obstruction and the consequent air trapping (pulsion mechanism). This phenomenon is easy to explain, considering that during the acute attack of asthma, a greater force is needed to maintain and promote the airways patency. An impairment of matrix metalloproteinases (MMPs) and tissue inhibitor of MMPs, with the consequent degradation of the extracellular matrix, the tissue destruction and the airways remodeling with loss of the physiological structure have been demonstrated both in asthma and in bronchiectasis [111]. In any case, the rela-

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tionship between inflammatory markers and the direct structural damage is still unclear [112].

In conclusion, it is possible to hypothesize that stagnant mucus, associated with the presence of pathogens at small airways level and a lower activity of phagocytosis observed in asthmatic patients [113], could play a role in the pathogenesis and maintenance of bronchiectasis [114], and could trigger a vicious circle similar to the Cole one [115], where the chronic and mainly eosinophilic inflammation represents the *primum movens* of the bronchial remodeling. This remodeling is then responsible for the onset of bronchiectasis through a chronic infection and an imbalance between MMPs [18], which could cause in the long term a tissue destruction and, consequently, airways remodeling associated with bronchial damages (bronchial enlargements) [7, 11, 85]; these structural alterations can evolve to true bronchiectasis when frequent exacerbations occur [21].

Due to the fact that mucus is a "treatable trait," it is evident that the management of bronchial secretions must be considered in asthmatic patients with bronchiectasis in order to prevent functional and radiological impairments of the respiratory tract and to reduce the number of exacerbations.

Common Causes of Asthma and Bronchiectasis

We need to take into account that some clinical conditions and/or diseases, such as gastroesophageal reflux disease (GERD), immune deficits, chronic rhinosinusitis, and allergic bronchopulmonary aspergillosis (ABPA), represent common elements in the etiopathogenesis of both bronchial asthma and bronchiectasis and possible irritative triggers, as reported by Porsbjerg [4] and Lonni [72].

Gastroesophageal Reflux Disease

GERD is defined as a pool of symptoms associated with the acid reflux into the esophagus. The most frequent symptoms are dyspepsia, retrosternal heartburn, and epigastric pain, but many patients often remain asymptomatic. The frequency of GERD in asthmatic patients ranges from 17 to 74% [116–118], and the disease is probably due a direct inhalation of acids in the airways [119]. Although the true mechanism by which GERD worsens asthmatic symptoms is still controversial and unclear, the same process seems to be responsible for the onset and the maintenance of bronchiectasis as well [120], where the incidence of GERD is higher than in healthy population, and it is associated with a higher impairment of the respiratory function [121]. Even if more studies are needed for better understanding the interaction between GERD and asthma/bronchiectasis, we can hypothesize that GERD is involved in the onset of both bronchiectasis, through a "digestive" mechanism induced by gastric acid and enzymes followed by an injury of bronchial wall and epithelium, and asthma itself, through reflex and reflux mechanisms. Therefore, the exacerbation of asthmatic symptoms may probably be due to a direct irritative action, or an indirect action through the development of bronchiectasis.

Immune System Deficiency

It is well known that the immune system has a pivotal role in the pathogenesis and maintenance of respiratory diseases and that dysfunctions of the innate and acquired defence mechanisms make these diseases difficult-to-treat and severe from a clinical point of view.

Immunoglobulins (Ig) and a deficit of IgG subgroups can be a common element for the etiopathogenesis of bronchial asthma and bronchiectasis, able to determine an impairment of the immune response against pathogens [120–123]. In fact, many cases of bronchiectasis are considered related to immunological deficits such as the common variable immunodeficiency, showing also functional patterns very similar to those of bronchial asthma [72]. Furthermore, the presence of immunodeficiencies can often cause functional patterns similar to those of asthma [49], generating further diagnostic problems.

This impairment can be caused not only by a primary IgG deficit [124] but also by a chronic use of corticosteroids, as observed in patients with persistent severe bronchial asthma [16]. In this latter case, however, it is still uncertain whether the association between Ig deficiency and disease severity is a consequence of the prolonged use of steroids or it causes the severity of the disease itself. In any case, the impaired production of Igs (especially IgG1) and the consequent dysfunction of the immune system in asthmatic patients could favor the onset of bronchiectasis through the Cole cycle, with a further worsening of the clinical conditions and the natural history of the disease.

Corticosteroids could stimulate the bacterial colonization, a typical feature of bronchiectasis, increase the number of exacerbations, and the production of purulent mucus, as observed in COPD patients [125, 126] and bronchiectasis [127]. The study by Lujan et al. [16] showed an increased number of bronchiectasis in patients with severe asthma treated with corticosteroids (20%) with respect to patients nontreated with these drugs. However,

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this difference was not related to Igs levels but to the disease severity consequent to a higher level of inflammation and remodeling, an impairment of the mucociliar clearance and a progressive and more severe obstruction.

Allergic Bronchopulmonary Aspergillosis

Another common risk factor for severe bronchial asthma and bronchiectasis is ABPA, defined as a hypersensitivity reaction against *Aspergillus fumigatus*, a mycete frequently isolated in patients with bronchial asthma, cystic fibrosis, and bronchiectasis non associated with cystic fibrosis [128, 129], characterized by a mainly Th2-mediate immune response [130]. Although ABPA is a relatively rare disease, with a prevalence of 0.7–3.5% in patients with asthma and 5–25% in patients with severe persistent asthma [15], this comorbidity must be always considered during the evaluation of difficult-to-treat asthma. Asthmatic patients with ABPA have a poor symptoms control, mucus hypersecretion, and frequent exacerbations with the consequent functional decline and an impaired quality of life [15]. An amazing feature of asthmatic patients with ABPA is the absence of atopic diseases, such as allergic rhinitis, urticarial, and eczema: this confirms the high heterogeneity of severe asthma. Bronchiectasis, especially the central ones, are a pathognomonic element for ABPA: for this reason, a radiological screening for bronchiectasis seems reasonable in patients with severe asthma, in order to identify patients at risk of developing ABPA or for early diagnosis [131].

Chronic Rhinosinusitis

Chronic rhinosinusitis (i.e., present for at least 12 weeks) is an inflammatory disease of nose and paranasal sinuses associated with clinical symptoms such as nasal congestion, retro-nasal drainage, facial pain, and ipo/anosmia. These symptoms are often endoscopically and radiologically confirmed (sinuses CT scan) [132]. Rhinosinusitis is frequently associated with asthma and allergy [133] because they have common etiopathogenetic features [4, 132, 134–136]. The frequents of rhinosinusitis in bronchiectasis range from 34 to 75% [132, 137–139] even in absence of ciliary dyskinesia [140]; besides, rhinosinusitis is considered an important risk factor for exacerbations of lower respiratory infections [141–143], even if the mechanism is still unknown, as well as a worsening factor of quality of life [144]. The treatment of rhinosinusitis is both medical (i.e., topical corticosteroids, saline solutions) and surgical; the concomitant presence of asthma or bronchiectasis as "treatable traits" must be considered.

Treatment

The recognizing of the association of asthma and bronchiectasis is important not only for diagnostic and prognostic purposes but for the therapeutic strategy too. Actually, the treatment recommendations of the National Asthma Education and Prevention Program are the following: adding oral steroids to the maximal therapy in patients with severe persistent bronchial asthma; anti-IgE drugs in allergic patients; new anti-IL-5, and anti-IL-13 in hypereosinophilic patients. According to the Guidelines [1], steroid therapy represents the gold standard for patients with bronchial asthma. On the contrary, Guidelines [21, 22] do not recommend inhaled corticosteroids in bronchiectasis, but this does not change the therapy of asthma and COPD as per individual guidelines [1, 145]. In fact, based on clinical studies performed in COPD patients [145–147] and patients with bronchiectasis [127], the use of inhaled steroids is controversial and seems to be related to an increased risk of hospitalizations and infections and to higher bacterial loads at airways level, even if this is not clearly associated with an increase of mortality [148]. Patients with steroid-dependent severe asthma and bronchiectasis [16] showed reduced levels of Igs respect to nonsteroid-dependent patients and, consequently, a higher susceptibility to bacterial infections.

The current drug therapy for asthma, generally administered by inhalation route, is often not sufficient in patients with asthma and bronchiectasis, because bronchiectasis is often associated with chronic bacterial infections. It is therefore appropriate to consider the treatment of the single disease, as stated by the Guidelines [21, 22], a treatment for a better management of the secretions, such as the airway clearance technique or pulmonary rehabilitation, or a better control of infections, such as long-term antibiotic or anti-inflammatory therapy, must be added to the standard therapy.

Bronchiectasis is caused by a mainly neutrophilic inflammation and bronchial asthma by a mainly eosinophilic inflammation. This latter inflammation can be controlled with corticosteroid therapy, while macrolides can reduce the number of exacerbations in the neutrophilic form. The fact that a group of asthmatic patients who do not respond to the usual steroid therapy can benefit from antibiotic therapy, leads us to support the hypothesis that this phenotype of patients could have bronchiectasis. Several studies show that a long-term therapy with macrolides is able to reduce the number of exacerbations, as well as the functional decline, and to improve the quality of life of patients with bronchiectasis [149–151].

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This could be also true for patients with bronchial asthma and associated bronchiectasis, as already reported by the AMAZES study [152], highlighting the importance of both acute and chronic treatment with macrolides.

The anti-IL-5 biologic drugs, such as mepolizumab, benralizumab, and reslizumab, which act reducing the number of peripheral eosinophils and, consequently, the eosinophilic inflammatory response, can also be useful for the management of patients with severe asthma. Recently, mepolizumab was widely used for the treatment of patients with severe asthma, including cases of severe asthma associated with bronchiectasis, even if their number is limited [153]: the effects of this drug on eosinophilic inflammation allowed to improve the management of these patients in terms of control of asthma and bronchiectasis exacerbations. Further studies on patients with asthma and bronchiectasis are needed for identifying and confirming the role of eosinophils in the pathogenesis and the maintenance of the inflammatory process responsible for the bronchial remodeling, as well as the therapeutic efficacy of an anti-eosinophilic treatment.

Conclusion

In conclusion, the concomitant association of bronchiectasis and bronchial asthma should be suspected and investigated in patients with severe asthma, purulent sputum, frequent exacerbations, and unresponsive to the standard therapy. Really, this combination could identify a radiological and functional phenotype often characterized by a more severe disease, worse outcomes, and functional decline, which must be readily recognized in order to choose the most appropriate therapeutic approach. The correct treatment of bronchiectasis and the better management of mucus, representing "treatable traits," can potentially improve the management of bronchial asthma, prevent the onset of exacerbations as well the functional decline, and reduce health costs.

Further larger studies are needed for precisely defining the real prevalence of bronchiectasis in asthma; longitudinal studies can also help us to better identify a possible correlation between asthma and bronchiectasis and other prognostic factors such as mortality and risk of exacerbations/hospitalizations. Other aspects to be considered in future studies could be the evaluation of biomarkers potentially useful for the choice of therapeutic strategies, such as the role of eosinophils in patients with asthma bronchiectasis.

Disclosure Statement

The authors declare no conflicts of interest associated with this study.

Funding Sources

The authors have not received any funding for this study.

Author Contributions

N.C.: had the final responsibility for the decision to submit the paper for publication. All authors are responsible for the study concept and design. C.C., S.F., and R.C.: are responsible for acquisition of data. All authors are responsible for analysis or interpretation of data, drafting of the manuscript, and manuscript revision.

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