



INVITED REVIEW SERIES:  
PAEDIATRIC AND ADULT BRONCHIECTASIS  
SERIES EDITORS: ADAM T. HILL AND ANNE B. CHANG

## Paediatric and adult bronchiectasis: Specific management with coexisting asthma, COPD, rheumatological disease and inflammatory bowel disease

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### ABSTRACT

Bronchiectasis, conventionally defined as irreversible dilatation of the bronchial tree, is generally suspected on a clinical basis and confirmed by means of chest high-resolution computed tomography. Clinical manifestations, including chronic productive cough and endobronchial suppuration with persistent chest infection and inflammation, may deeply affect quality of life, both in children/adolescents and adults. Despite many cases being idiopathic or post-infectious, a number of specific aetiologies have been traditionally associated with bronchiectasis, such as cystic fibrosis (CF), primary ciliary dyskinesia or immunodeficiencies. Nevertheless, bronchiectasis may also develop in patients with bronchial asthma; chronic obstructive pulmonary disease; and, less commonly, rheumatological disorders and inflammatory bowel diseases. Available literature on the development of bronchiectasis in these conditions and on its management is limited, particularly in children. However, bronchiectasis may complicate the clinical course of the underlying condition at any age, and appropriate management requires an integration of multiple skills in a team of complementary experts to provide the most appropriate care to affected children and adolescents. The present review aims at summarizing the current knowledge and available evidence on the management of bronchiectasis in the other conditions mentioned and focuses on the new therapeutic strategies that are emerging as promising tools for improving patients' quality of life.

**Key words:** asthma, bronchiectasis, chronic obstructive pulmonary disease, inflammatory bowel disease, rheumatological disease.

### INTRODUCTION

Bronchiectasis is a pathological or radiological entity characterized by irreversible bronchial dilatation with clinical manifestations that include chronic cough, sputum production and frequent infectious exacerbations.<sup>1,2</sup> As such, bronchiectasis represents a heterogeneous compilation of aetiologies with an equally protean set of clinical manifestations and symptoms. These presentations have been characterized more recently by a wide range of phenotypes and endotypes.<sup>3,4</sup>

High-resolution computed tomography (HRCT) represents the gold standard for diagnosis both in children and adults, and despite existing controversies in diagnostic criteria for affected children, some key radiological features are commonly accepted for definition. These are mainly represented by an increased bronchoarterial ratio, bronchial wall thickening, lack of bronchial tapering from central to periphery and mucous plugging.<sup>5</sup>

Despite generally being considered irreversible, computed tomography (CT)-based studies suggest that early cylindrical bronchiectasis can potentially revert in children.<sup>6</sup>

Historically, and in most recently published series, the majority of clinical bronchiectasis has been linked aetiologically to either idiopathic or post-infectious causes. There are, however, specific aetiologies associated with bronchiectasis that include, but are not limited to, CF, primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis (ABPA), alpha-1-antitrypsin deficiency, aspiration, immunodeficiency, asthma (non-ABPA), chronic obstructive pulmonary disease (COPD), rheumatological disease (RD) and inflammatory bowel disease (IBD).<sup>2,7</sup> With the exception of CF-associated bronchiectasis, the heterogeneity of presentations and natural disease courses implicit to bronchiectasis has likely contributed to the observed varied clinical responses to therapeutic interventions, including results from the recent phase III inhaled antibiotic clinical studies that have consistently not met the primary endpoints.<sup>8-11</sup> The extent to which the various

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Received 10 March 2019; invited to revise 18 April 2019; revised 18 May 2019; accepted 21 May 2019

bronchiectatic phenotypes and endotypes respond to specific treatment is essentially unknown and is a matter of intense research interest and investigation. This is particularly true for affected children as studies characterizing large paediatric cohorts of bronchiectasis sharing the same aetiology are limited, making this a research priority in this field.

It is the limited purpose of this study to review the current available rationale of the specific management of bronchiectasis in association with other airways diseases, including COPD and asthma, as well as RD and IBD in children and adults. Specific Management of bronchiectasis has been recently addressed in international guidelines.<sup>12,13</sup>

## BRONCHIECTASIS AND COEXISTING ASTHMA AND COPD IN CHILDREN

As many disorders characterized by recurrent-to-persistent bronchial injury may eventually result in the development of bronchiectasis, multiple causes of paediatric bronchiectasis have been reported.<sup>14</sup> Regrettably, limited access to diagnostic technology in some areas, especially in developing countries, makes a precise assessment of aetiology still poorly defined, and therefore, even a detailed diagnostic work-up may be inconclusive in up to 50% of patients.<sup>15–18</sup> Nevertheless, identifying aetiology is very relevant as it can influence patients' management, including investigations for specific causes, disease severity evaluation and referral to specialized centres for the longitudinal follow-up and start of treatment.

Among the possible causes of bronchiectasis, asthma should always be ruled out given the high prevalence of both atopic and non-atopic diseases within the paediatric population. In asthma, major structural abnormalities consist of thickening of the conducting airways with luminal narrowing and excessive mucous production associated with inflammatory exudates, and these changes are very relevant, especially in patients with uncontrolled or severe asthma.<sup>19</sup> Thick and/or purulent secretions can cause progressive obstruction and bronchial wall damage that are supposed to be the major determinants of bronchial dilatation,<sup>20</sup> but an additional mechanism leading to the development of segmental atelectasis with increased negative intrapleural pressure, progressive traction on bronchial walls, and, in turn, bronchial dilation should also be considered.<sup>21</sup> Bronchial mucous plugging associated with the dilatation of bronchial mucosal blood vessels, congestion and wall oedema are also consistently reported features of fatal asthma in young patients,<sup>22</sup> but the reasons why bronchiectasis develops in some but not all children with asthma is still unclear. A study from Korea concluded that patients with asthma and evidence of bronchiectasis should be monitored carefully because of the increased number of exacerbations and greater use of systemic steroids, but this population did not include children or adolescents.<sup>23,24</sup> Undoubtedly, children with poor asthma control have an increased risk of severe exacerbations and progressive loss of lung function, and bronchial wall thickening on HRCT may constitute an additional criterion of asthma severity in

this subset of patients.<sup>25</sup> Nevertheless, although a relationship between reticular basement membrane thickness and bronchial wall thickness on HRCT was found in adults with asthma, this relationship does not appear to hold true in children with severe uncontrolled asthma<sup>26</sup>; thus, there is poor evidence to recommend the routine use of HRCT in children with severe asthma unless other causes of bronchiectasis erroneously attributed to asthma are excluded.<sup>27</sup>

Among smoking adults, COPD is extremely common over 40 years of age and represents a major worldwide public health concern. In adults, COPD is frequently associated with bronchiectasis, and patients actually constitute a subgroup with more severe disease and more frequent asthma exacerbations. Although COPD is not included among the chronic pulmonary disorders traditionally described in children or adolescents, the term *chronic obstructive pulmonary disease* in children has been coined to indicate a cluster of disorders unrelated to active long-term smoking that may result in progressive lung structure derangements and persistent airflow limitation in adult life.<sup>28</sup> Notably, there is increasing evidence that most adult chronic obstructive lung diseases have at least part of their origins in early life, with individuals entering adulthood with incomplete lung growth being at increased risk of COPD, even in the absence of rapid lung function decline.<sup>29</sup> The asthma-COPD overlap syndrome (ACOS), with persistent airflow limitation and several features usually associated either with asthma or with COPD, has also gained interest in paediatrics.<sup>30</sup> As the ACOS may also include bronchiectasis in the bronchiectasis-associated subgroup (BCOS), there is increasing evidence that bronchiectasis may also complicate asthma in children or adolescents with persistent impaired lung function, thus confirming that ACOS may develop at younger ages as well.<sup>31,32</sup>

Children with uncontrolled asthma require high-dose inhaled corticosteroids (ICS) in association with a long-acting  $\beta_2$ -agonist (LABA) plus oral leukotriene receptor antagonist or additional strategies, particularly anti-IgE treatment.<sup>33</sup> There are no trials of ICS in children or adolescents with non-CF, bronchiectasis-associated asthma or COPD, and the existing adult studies show minimal and, in most cases, no clinically significant benefits.<sup>34</sup> The recent European Respiratory Society (ERS) guidelines for the management of adult bronchiectasis concluded that ICS do not have a role in the routine management of adult bronchiectasis<sup>12</sup> but also that, in the absence of specific data, the presence of bronchiectasis alone should not lead to a decision to withdraw ICS from patients with established asthma. Randomized controlled trials of ICS in children with bronchiectasis who are naïve to ICS are recommended to define the true utility of this therapy.

## BRONCHIECTASIS AND COEXISTING ASTHMA AND COPD IN ADULTS

Perhaps the murkiest assignment of association of adult bronchiectasis with coexisting diseases is the connection with other airways diseases, including asthma and COPD.<sup>35</sup> In particular, 4–72% of patients with

severe COPD have been recently reported to have bronchiectasis on CT, with similar frequencies (20–30%) reported in cohorts with severe or uncontrolled asthma.<sup>36</sup> For the purposes of this review, ABPA will be considered a distinct and separate entity aside from asthma and will not be further discussed. As described above, the classification between different airway diseases can often represent a semantic and diagnostic dilemma. The relatively high prevalence of asthma and COPD in adult populations underscores the importance of clarifying the need for proper classifications. Standard definitions for adults with a diagnosis of asthma or COPD have been proposed by global initiative statements.<sup>37</sup> More recently, interest in the definition of the ACOS has been increasingly explored, with many caveats and unknowns still present.<sup>38,39</sup> To a large extent, the importance of definition becomes as much as an endotype distinction as it does a phenotype distinction.<sup>40–42</sup> The ACOS profile has carried with it a negative impact on the natural course of disease.<sup>43</sup> These distinctions have an additional important impact on the approach to treatment, which has also been increasingly addressed recently. Many have advocated for adhering to the treatment of asthma plus COPD strategies rather than either alone for those individuals who can be classified as ACOS.

Most series of primary adult bronchiectasis patients include a diagnosis of COPD and/or asthma widely varying in numbers. Characteristic inflammatory profiles of bronchiectasis, to a large extent, will not surprisingly overlap with COPD and, in some instances, asthma as well as the ACOS.<sup>44</sup> The rate of COPD as an accompanying diagnosis to a primary diagnosis of bronchiectasis is often higher than that of asthma. In a recent series of European bronchiectasis patients as part of the FRIENDS cohort, asthma was reported in 3% and COPD in 15%.<sup>7</sup> Previous series have reported numbers as high as 27% of bronchiectasis patients in Hong Kong.<sup>45</sup> In contrast, data taken from the US Registry estimated that 29% and 20% of patients with bronchiectasis enrolled in the US Bronchiectasis and NTM Research Registry had asthma and COPD, respectively.<sup>46</sup> From a different perspective, the numbers of adult asthma and COPD patients with bronchiectasis tend to be much higher, especially with advanced severity of disease. It has been estimated that between 8% and 59% of COPD patients and between 12% and 68% of asthma patients have bronchiectasis of varying degrees.<sup>12,35</sup>

Part of the dilemma for clinicians, as well as clinical investigators, is to discern whether one, two or three diagnoses (bronchiectasis, asthma and/or COPD) are present. Moreover, it may be equally challenging to classify bronchiectasis with asthma or COPD as overlap patients versus asthma and COPD with bronchiectasis. Being a structural lesion, bronchiectasis is defined by relatively strict radiological diagnostic criteria, such as the ratio of the diameters of bronchial lumen and adjacent artery. Nevertheless, it has been argued that, particularly in smokers, interpretation of this parameter should be careful as it might be sensitive to changes in pulmonary arteries.<sup>47</sup> The implication of course is to understand whether specific therapies directed towards asthma,

COPD or bronchiectasis are applicable. No more therapeutic intervention illustrates this more poignantly as ICS. In fact, there is little direct evidence to support the use of ICS in adult bronchiectasis patients, and ICS are not recommended other than when indicated for reasons of asthma or, in some instances, for COPD as standard of care.<sup>12</sup> This need for reconciliation of ICS use is borne out of observing that 39% of bronchiectasis patients in the US Registry are using ICS.<sup>46</sup> Furthermore, the relative use of non-pharmacological, as well as other pharmacological, therapies is equally unclear, including mucolytic therapies such as nebulized hypertonic saline, N-acetyl cysteine, inhaled mannitol and long-acting bronchodilators including LABA and long-acting muscarinic agonists (LAMA). Macrolide use in adult bronchiectasis patients with coexisting COPD or asthma represents an even larger dilemma. Even though macrolides have been shown to be effective in (non-CF) bronchiectasis<sup>48–50</sup> and are recommended for select frequent exacerbator populations,<sup>12</sup> the beneficial use of macrolides in adult COPD patients and, to even a lesser extent, in asthma patients is less clear.<sup>51–54</sup>

There are little data available addressing best therapeutic strategies in adult bronchiectasis overlap patients with coexisting asthma and/or COPD. Further investigations are sorely needed. In the interim, clinicians are probably best served to unbundle specific classifications with reliance on endotype and treatable traits tied to bronchiectasis to determine the best treatment on a case-by-case basis.<sup>55</sup> In an approach to the individual patient, a concept begins to emerge characterized recently with a label of precision medicine.<sup>56</sup>

The clinical investigator, on the other hand, during clinical trial design in the future is charged with an imperative to a priori address the inevitable issues of heterogeneity of endotype, phenotype and treatable traits of adult bronchiectasis patients with or without coexisting asthma and COPD to make meaningful observations.

In summary, what is the best approach to the treatment of adult bronchiectasis patients with coexisting asthma and COPD? It is our opinion that one must carefully assess the phenotype, endotype and treatable traits on an individualized basis to best achieve an individualized therapeutic programme through precision medicine. As one example, an adult patient with bronchiectasis and established symptomatic moderate to severe asthma, including productive cough with mucous plugging noted on chest imaging, would be a candidate for asthma triple therapy with LABA, LAMA and ICS, as well as airway clearance programmes including trials of hypertonic saline and non-pharmacological therapies as recommended for bronchiectasis patients in accepted guidelines. Likewise, if frequent exacerbations with or without *Pseudomonas* are noted, considerations of additional intervention according to guideline recommendations may be applicable despite the lack of data to support this specific cohort of overlap patients.<sup>12</sup> Incorporating endotype and treatable traits in a treatment programme would be equally applicable for adult bronchiectasis patients with coexisting COPD.<sup>35</sup>

Future investigations and research are needed to specifically address the impact of the integration of phenotype, endotype and treatable traits in adult bronchiectasis patients with coexisting asthma and COPD if advancing the science of bronchiectasis and closing knowledge gaps are to occur.

## BRONCHIECTASIS AND COEXISTING RD IN CHILDREN

Pulmonary involvement is frequently reported in paediatric RD, a heterogeneous group of systemic inflammatory diseases of autoimmune origin that include juvenile rheumatoid arthritis (RA), polymyositis, systemic lupus erythematosus, scleroderma, dermatomyositis, Sjogren's syndrome, Wegener's granulomatosis and systemic vasculitis.<sup>57</sup>

Clinical respiratory manifestations of RD generally begin with an infectious event that triggers the activation of the inflammatory cascade, eventually resulting in lung tissue repair with fibroblasts and collagen deposition. The histopathology of the lung mainly includes features of interstitial disease with associated vascular abnormalities and development of fibrosis, even though the frequency of these findings is extremely variable depending on the specific underlying RD. In addition to this, as in some RDs conducting airways are involved, bronchiectasis may develop, and then the association between the two conditions should be taken into account in the management of affected patients.

Most of the literature on RD-associated bronchiectasis includes adult studies, and only few anecdotal reports or small case series include children or adolescents. This severely restricts the literature search on this issue. The association between bronchiectasis and RD is best described with juvenile RA. The prevalence of bronchiectasis in juvenile RA varies considerably in studies, with a prevalence up to 70% in adulthood and significantly fewer cases among the paediatric population, even though the absence of specific recommendations on the frequency of chest CT in these patients likely means that a number of asymptomatic patients remain undiagnosed.<sup>57</sup> Of relevance is the observation that, in most cases, respiratory symptoms start during childhood or adolescence and frankly precede the first clinical appearance of arthritis.<sup>58</sup> In most cases, mixed functional obstructive and restrictive impairment (the latter due to overt interstitial lung disease) may develop, and at that stage, chronic respiratory insufficiency is prominent.<sup>59</sup> Most of the authors agree that, in juvenile RA, the *primum movens* is the inflammation that persistently damages the bronchial wall and then, combined with interstitial fibrosis, forces the bronchi to become dilated, leading to traction bronchiectasis.<sup>60</sup> Dilated bronchi may host respiratory pathogens, and recurrent or permanent local infection also related to secondary immunosuppression results in bronchial suppuration. A study of adults with RA not including children or adolescents demonstrated that bronchiectasis is an unusual but potent model for the induction of autoimmunity by bacterial infection in the

lung, thus suggesting that the prognosis of the disease may be worse when bronchiectasis develops.<sup>61</sup>

Paediatric RD other than juvenile RA is less frequently associated with bronchiectasis and includes scleroderma, Sjogren's syndrome, polymyositis and vasculitis. In affected patients, traction bronchiectasis is described, but again, paediatric cases are significantly less reported than adults.<sup>62</sup> A recent study of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis not including children or adolescents found that bronchiectasis, documented in 38% of the cases, did not worsen patients' outcome when anti-myeloperoxidase anti-neutrophil cytoplasm antibody-associated vasculitis was expressed.<sup>63</sup> Overall, when bronchiectasis is documented in association with RD, the outcome of the underlying disorder seems to be worse than without RD.<sup>57</sup> In addition to this, the immune dysregulation due to immunosuppressive drugs likely results in more infectious complications, namely, recurrent pneumonia, and this significantly increases the risk of developing bronchiectasis. It has also been postulated that, in adults with autoimmunity disorders such as polymyositis, respiratory pathogens may induce autoimmunity and/or exacerbate the disease, and bronchiectasis may eventually develop.<sup>64</sup>

## BRONCHIECTASIS AND COEXISTING RD IN ADULTS

RD and bronchiectasis are no less confounding in adults than children, although as noted above, there are more data available. Of the connective tissues diseases, including RA, Sjogren's syndrome, scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus and mixed connective tissue disease, interstitial lung disease is the most common pulmonary manifestation.<sup>65</sup> Traction bronchiectasis associated with the interstitial disease will not be a focus of this discussion, although, if present and if clinical features resemble that of primary bronchiectasis, general recommendations may be applied as have been suggested by international guidelines.<sup>12</sup> It is interesting that, as mentioned above, the systemic inflammatory responses of RA and responses associated with specific airway infections in bronchiectasis may predispose to the development of bronchiectasis and RA, respectively.<sup>66,67</sup>

The occurrence of RA with bronchiectasis is generally lower than the association with COPD. In a recent series from six different European centre cohorts of bronchiectasis, 1–23% of patients also carried a diagnosis of RA,<sup>66</sup> which is not dissimilar to the 8% of bronchiectasis patients also having RD in the US registry.<sup>46</sup> Others have estimated the prevalence to be between 3% and 5.2%<sup>15,68</sup> with the exception being a rate of 28.6% in a US urban cohort of African-Americans.<sup>69</sup> The presence of any bronchiectasis, including by HRCT, is otherwise common in RA patients and is estimated to be between 3% and 62% as reported by a number of series of patients.<sup>67</sup> Interestingly, a lower incidence appeared to be unique for Chinese patients.<sup>70</sup> The demographics and severity based on the Bronchiectasis Severity Index (BSI) in the European cohorts of bronchiectasis with RA were similar to those

bronchiectasis patients without RA or other causes of bronchiectasis other than COPD. The bronchiectasis COPD cohort in this same European series had more *Pseudomonas* infection, male predominance, lower forced expiratory volume in 1 s (FEV<sub>1</sub>) and higher BSI scores. Moreover, the overall 5-year mortality in comparison between bronchiectasis, bronchiectasis with RA and bronchiectasis with COPD increased from 8.6% to 18% to 28.5%, respectively.<sup>66</sup> The increased mortality associated with the presence of RA in bronchiectasis patients extended across all BSI scores. For comparison, increased 5-year mortality was seen in RA-interstitial lung disease patients (63.4%) compared to RA-bronchiectasis (12.9%) in a separate series.<sup>71</sup>

Disease-modifying anti-rheumatic drugs (DMARD) including biologic and non-biologic agents are commonly used in RA patients. No changes in DMARD use were seen in RA patients with or without bronchiectasis.<sup>66</sup> Although many of the biologic and non-biologic DMARD can increase the risk of infection and, in some instances (e.g. methotrexate or biologic), have well-described potential pulmonary side effects from the medication itself, there is no clear predisposition of DMARD being independently associated with developing bronchiectasis.<sup>67</sup>

Treatment implications dictate that adult bronchiectasis patients with coexisting RA are best cared for by a collaboration of pulmonary physician as well as rheumatologist. There appears to be no specific therapies for bronchiectasis patients based on the presence or absence of RA. Nonetheless, the use of many of the biologic and non-biologic agents needed attention and precautions, including *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, as well as screening for non-tuberculous mycobacteria (NTM) or latent tuberculosis (TB) infection (LTBI). Moreover, airway clearance appears to be no less important than in a general adult bronchiectasis population. For those adult bronchiectasis patients with RA and frequent chest exacerbations, use of inhaled antibiotics, macrolide or other suppressive antibiotic may be reasonable to consider following international guidelines.<sup>12</sup> Best practice in our opinion requires ample communication and cooperation between pulmonary and rheumatology physicians, as well as other care team members including chest physiotherapists, nurses and pharmacists when involved.

## BRONCHIECTASIS AND COEXISTING IBD IN CHILDREN

IBD, namely Crohn's disease (CD) and ulcerative colitis (UC), are chronic disorders primarily affecting the gastrointestinal tract and differ in the distribution of inflammatory lesions, histological features and clinical presentation. IBD pathogenesis likely moves from a complex interaction between genetic, environmental and immunoregulatory factors.<sup>72</sup> Extra-intestinal manifestations are observed in both conditions but are far more frequent in CD, which can be observed in approximately 25–40% of affected subjects.<sup>73</sup>

Given its low prevalence, bronchopulmonary involvement is seldom considered a potential expression of IBD, and therefore, it is often overlooked,

particularly in children. Nevertheless, lung involvement may be reasonably expected due to the structural similarities between gut and bronchial tree and their common origin from the primitive foregut.<sup>72</sup>

Despite the reported prevalence of pulmonary manifestations being similar between UC and CD,<sup>74</sup> parenchymal abnormalities and large airway disease seem to be more commonly associated with UC,<sup>75</sup> even though available data from adult studies and large paediatric populations have not been investigated for lung involvement.

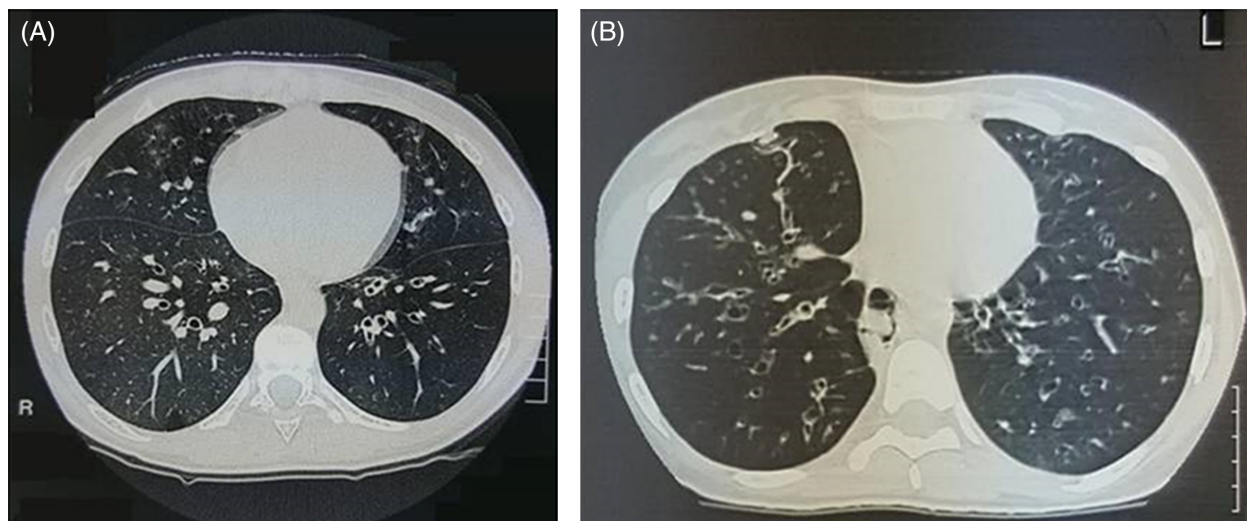
Non-specific airway inflammation is the most frequent pulmonary manifestation in IBD and may lead to the development of bronchiolitis obliterans, organizing pneumonia and bronchiectasis.<sup>76</sup> Bronchial hyper-responsiveness has been considered an expression of IBD subclinical airway inflammation, a phenomenon that can be responsible for the development of various pulmonary manifestations, particularly in CD.<sup>77</sup>

In children with IBD, pulmonary involvement is generally much more uncommon than in adults<sup>78</sup> and has been more frequently described in CD.<sup>79–81</sup> Bronchiectasis has been described in up to 66% of IBD adults with airway disease, whereas chronic bronchitis and suppurative large airway disease without airway dilation represent less common manifestations.<sup>82</sup> Nevertheless, the reported prevalence is deeply affected by patient selection, as shown by two adult studies that detected bronchiectasis and other pulmonary abnormalities at chest CT in the majority of the considered subjects, probably due to the presence of respiratory symptoms within the selection criteria.<sup>83</sup> On the other hand, a paediatric study assessing lung disease by means of HRCT in 32 IBD subjects with no respiratory symptoms found mild bronchiectasis only in one child.<sup>78</sup>

Finally, an interesting aspect that is emerging in IBD literature is the possibility of treating CD-associated pulmonary lesions by means of infliximab, the widely used anti-TNF- $\alpha$  monoclonal antibody approved for CD treatment about 20 years ago. The few described cases involve both adults<sup>84</sup> and children,<sup>85</sup> and structural abnormalities that proved responsive to infliximab included bronchiolitis obliterans, organizing pneumonias and non-caseating granulomas.

Early detection of bronchiectasis, as well as of other associated pulmonary complications, would hopefully help to start specialized management of the disease and improve the final outcome. The integration of several specialists dedicated to airway disease management in a multidisciplinary team including paediatric rheumatologists, gastroenterologists, allergists, pulmonologists, radiologists and respiratory therapists is essential to provide the most appropriate care to affected children and adolescents.

Unfortunately, indications or recommendations specifically made for the management of bronchiectasis associated with IBD are not available as is the case for coexisting asthma, COPD or RA. The identification of bronchiectasis generally relies on HRCT, a technique that has significantly increased the sensitivity and monitoring of the diagnosis (Fig. 1). Evidence of bronchiectasis requires microbiological surveillance by means of regular sputum cultures in order to provide prompt antibiotic treatment of chest infections. In daily practice, core prescriptions should include airway clearance



**Figure 1** High-resolution computed tomography scans showing diffuse bronchiectasis in the lower lobes from (A) a 16-year-old-girl with atopic moderate-to-severe bronchial asthma and (B) an 18-year-old-girl with polymyositis.

techniques and pulmonary rehabilitation programmes, as suggested in most guidelines or consensus on adult or paediatric bronchiectasis.<sup>12,86</sup> As patients with bronchiectasis suffer from recurrent exacerbations, resulting in further destruction of the airways and reduced quality of life, a strategy addressed to reduce the level of bronchial infection by long-term use of macrolides might also be proposed to limit the risk of the persistent antigenic stimulation of bacterial infections increasing the underlying inflammatory processes.<sup>87</sup> As only very few studies in children have been published on this issue, future research is warranted to investigate the efficacy of macrolides in the paediatric population with bronchiectasis.<sup>88</sup>

## BRONCHIECTASIS AND COEXISTING IBD IN ADULTS

In two recent series of adult bronchiectasis patients, IBD has occurred even less often than the aforementioned groups of asthma, COPD and RA patients, ranging from 1% to 3% in the European series and 3% in the US Registry.<sup>7,46</sup> Bronchiectasis is comparable in frequency to other pulmonary manifestations in IBD patients including bronchiolitis with organizing pneumonia or chronic bronchitis<sup>74</sup> and ranges from 18% to 26%. These pulmonary manifestations in adults have generally been more commonly described with UC than with CD and may precede or follow (after years) a diagnosis of IBD. Interestingly, cases of bronchiectasis in both UC and CD have been described following colectomy with full preoperative pulmonary documentation, including clear lung fields in some.<sup>83,89</sup>

A special characteristic of the treatment approach worth highlighting for bronchiectasis and other pulmonary manifestations in IBD patients reflects the clinical improvement, often times marked, due to corticosteroids. Clinical experience and early reports have documented a consistent response to ICS (and systemic corticosteroids).<sup>74</sup> How these improvements correlate

to observations of elevated exhaled nitric oxide known to be present in some IBD patients remains unclear.<sup>90,91</sup>

Moreover, the increase in the use of biologics for the treatment of IBD compel the clinician to be vigilant regarding lung health hygiene, updating vaccines and screening for atypical pathogens as is carried out for RA patients on biologics, including but not limited to TB (LTBI) and NTM. Prophylaxis for PJP is no less important for IBD bronchiectasis patients when immunosuppressive therapies are used.

In any case, the approach to the treatment of adult bronchiectasis patients follows the aforementioned pattern of a general approach as outlined in international bronchiectasis guidelines. Special attention is also given to the role of treating symptomatic IBD bronchiectasis patients with corticosteroids. Other therapies, including biologics, along with required screening and monitoring may be needed for the treatment of IBD.<sup>92</sup>

## CONCLUSIONS

Over the past decades, several paediatric disorders associated with bronchiectasis have been identified. For many of these, new therapeutic strategies are currently available and have improved patients' life expectation as some offer the potential of a cure. Improvements in the quality and implementation of medical care would hopefully result in increased survival. Bronchiectasis is an important issue for paediatric patients with asthma or RD or IBD. It may complicate the clinical course at any age, and therefore, appropriate care is mandatory after taking into account the major characteristics of the disease (Table 1). The optimal integration of multiple skills in a team, including physicians with proven experience in the management of the underlying disease, as well as other complementary specialists, is ideal for improving the prognosis of associated bronchiectasis disease. These specialists have an opportunity to play an



**Table 1** Major structural and clinical characteristics of adult and paediatric bronchiectasis associated with other coexisting disorders

	Asthma and COPD	Rheumatological disorders	Inflammatory bowel diseases
Major structural abnormalities	Thickening of conducting airways Excessive mucous production Inflammatory exudates Dilatation of bronchial mucosal blood vessels with congestion and wall oedema	Associated vascular abnormalities, fibrosis (variable, depending on the specific underlying disease) Traction bronchiectasis	Diffuse bronchial wall thickening (with or without mucoid impaction) Bronchiectasis (cylindrical, varicose or cystic)
Implications for clinical management	Prolonged ICS therapy provides minimal or no benefit in the treatment of associated bronchiectasis Adults may benefit from asthma triple therapy (LABA, LAMA and ICS), as well as from airway clearance programmes In COPD-associated bronchiectasis, more <i>Pseudomonas</i> infections and worse respiratory function	Respiratory symptoms often start during childhood or adolescence, before rheumatological symptoms Possible induction of autoimmunity by lung bacterial infections may worsen final prognosis when bronchiectasis develops Immune dysregulation due to immunosuppressive drugs results in more infectious complications, thus increasing the risk of bronchiectasis	Pulmonary involvement less common in children than in adults, more frequently in CD than UC Microbiological surveillance needed for prompt treatment of chest infections Bronchiectasis in both UC and CD may follow colectomy even in the absence of preoperative lung impairment Increased susceptibility to opportunist infections due to immunosuppressive drugs

CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic agonist; UC, ulcerative colitis.

integrated role in the multidisciplinary approach to the diseases. Clinical suspicion, early recognition and prompt diagnosis of bronchiectasis associated with these challenging disorders are crucial as outcomes of treatment in many cases appear time-sensitive, with better results being achieved when intervention is initiated at a younger age or before the diseases has progressed.

Specific treatment approaches to the adult patient with bronchiectasis with coexisting asthma, COPD, RA and IBD are not dissimilar to the approach to children with few caveats. More specifically, patients with bronchiectasis with or without coexisting conditions need to be thoroughly evaluated, monitored regularly and subscribe to general lung health measures as outlined in international guidelines. Recommendations include the avoidance of tobacco exposure and air pollution, update of pneumococcal and influenza vaccines, formulation of an airway clearance regimen and regular physical activity with or without formal participation in pulmonary rehabilitation. Exacerbations should be treated promptly and completely, with special attention given to those patients who are frequent exacerbators, including consideration of nebulized antibiotics, macrolides or other suppressive therapy. Just as in the case of children, the approach to the adult with bronchiectasis and coexisting disease must be individualized, goals of treatment must be articulated, and expectations of risks and benefits mused be clarified in advance. Heavy reliance on patient education and use of a multidisciplinary team including nursing, respiratory therapy and pharmacy, as well as the respiratory

and other physicians involved, is likely to optimize treatment success and improve clinical course in our experience.

Aside from adhering to elements of standardized bronchiectasis treatment regimens, the treating respiratory physician is unequivocally compelled to identify specific coexisting conditions warranting consultation with non-respiratory providers including rheumatologists, allergists, immunologists and/or gastroenterologists.

Specific therapies will need to be matched to identify specific phenotypes, endotypes and treatable traits in an individualized manner consistent with precision medicine. Whether select adult bronchiectasis patients are candidates for corticosteroids for coexisting asthma or IBD, biologics for RA or IBD or other specific therapies remain a dynamic and ongoing process tied closely not only to the initial evaluation but also to the results of continued monitoring and additional changes in clinical status.

The clinical investigator, in contrast, has the most daunting challenge, and unequalled opportunity, starting from the position and understanding that most of the components of treatment programmes for bronchiectasis patients with coexisting diseases are based on little or no data. Moreover, the strength of recommendations is weak, even for those patients without coexisting conditions as suggested in recent guidelines. Clinical investigators, in addition, are charged to a priori define specific phenotypes, endotypes and treatable traits with respect to enrolment in clinical trials. Researchers must remain disciplined to not understate or over-extrapolate the heterogeneity of cohorts of

bronchiectasis patients commonly encountered with or without coexisting medical conditions, including but not limited to asthma, COPD, RA or IBD.

Although there admittedly remain more questions than answers regarding the best practice for paediatric and adult bronchiectasis patients with coexisting disease, current interest, enthusiasm and research funding are building a platform and creating a space for additional investigations to advance the science and address many of the gaps in knowledge to positively impact patient symptoms, natural course of the disease process and utilization of healthcare resources.

**Acknowledgements:** F.S. is member of EU-funded COST Action BEAT-PCD (BM1407).

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**Abbreviations:** ABPA, allergic bronchopulmonary aspergillosis; ACOS, asthma-COPD overlap syndrome; BSI, Bronchiectasis Severity Index; CD, Crohn's disease; CF, cystic fibrosis; CT, computed tomography; DMARD, disease-modifying anti-rheumatic drug; ERS, European Respiratory Society; IBD, inflammatory bowel disease; ICS, inhaled corticosteroid; Ig, immunoglobulin; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic agonist; LTBI, latent TB infection; NTM, non-tuberculous mycobacteria; PJP, *Pneumocystis jirovecii* pneumonia; RA, rheumatoid arthritis; RD, rheumatological disease; TB, tuberculosis; TNF- $\alpha$ , tumour necrosis factor alpha; UC, ulcerative colitis.

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