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REVIEW

Bronchiectasis and Other Chronic Airway Diseases: A Clinical-based Approach

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ABSTRACT

Bronchiectasis (BE) is a chronic respiratory disease with heterogeneous clinical manifestations. In a variable percentage of BE patients, chronic respiratory comorbidities can also be described, including asthma, chronic obstructive pulmonary disease (COPD), and chronic rhinosinusitis.

This association can lead to greater burden of symptoms, increased severity, and worse prognosis.The most recent guidelines, mostly based on expert opinions, state that all individuals with bronchiectasis should undergo a minimum bundle of tests which should be tailored to each patient. The determination of the etiology of bronchiectasis can guide treatment and influence prognosis.

Unfortunately, no official guidelines or recommendations have been produced yet to guide clinical management of these clinical associations.

This narrative review focuses on diagnosis and management of airways diseases in BE patients, trying to keep a practical approach to support decision making in a clinical setting.

Keywords: Airway diseases. Asthma. Bronchiectasis. Comorbidities. COPD.

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WHY SHOULD WE LOOK FOR AIRWAYS COMORBIDITIES IN BRONCHIECTASIS?

The spectrum of clinical manifestations in bronchiectasis (BE) is so wide that it is considered nowadays among the most heterogeneous and complex respiratory diseases. In 2016, a survey conducted over 1000 BE patients across Europe identified a list of 'hard-to-manage' clinical aspects including management of secretions, exacerbations, tiredness, shortness of breath and cough as the most frequent[1]. Unfortunately, these symptoms are largely unspecific since they are often described in most airways diseases. Additionally, the level of knowledge regarding this chronic condition is still poor compared with other more common ones such as asthma or chronic obstructive pulmonary disease (COPD). In fact, a few years ago, BE was still considered a rare disease and misdiagnosis was common since BE patients were often wrongly labelled with asthma or COPD, even in absence of any radiological assessment or compatible history of allergy or tobacco smoking. The main consequence was a considerable delay in diagnosis and proper treatment of BE[2,3]. Far from that, nowadays BE is not considered an orphan disease anymore and its prevalence, despite considerable geographic variations, is considered the third between respiratory diseases, after asthma and COPD[4].

In fact, the increasing awareness of the disease and of imaging in the assessment of lung diseases has brought to an increase of BE radiological diagnosis.

However, the presence of BE at computed tomography (CT) scan is not enough to define the disease: asymptomatic BE have been found in thoracic scans of healthy subjects[5] and different studies have revealed that a significant quote of patients with COPD or asthma can eventually develop bronchial enlargement as part of the natural history of the disease[6-8].

Today the definition of BE as a clinically significant chronic respiratory disease implies the presence of compatible clinical manifestations, radiological findings, and the ruling out of cystic fibrosis (CF), a condition that is easily confused with BE but requires different management[9]. However, the major impact of associated conditions on outcomes of BE patients has led to consider the assessment of comorbidities crucial to frame BE and to optimize clinical management and risk assessment (Fig. 1).

In fact, McDonnell et al.[10] have demonstrated the impact of comorbidities in determining long-term prognosis of BE being mortality risk much increased when multiple comorbidities are coexisting (Bronchiectasis Aetiology Comorbidity Index [BACI] score ≥ 6)[10] (Table 1).

However, some respiratory comorbidities seem to be particularly frequent in BE and represent a real challenge in terms of diagnosis, interpretation, and management at long-term[11]. The analysis of an international cohort of BE patients demonstrated that co-existing COPD is associated with a doubled risk of mortality[10], while another study showed an increase of 43% in the risk of exacerbation in this group of patients[12]. Similarly, the presence of asthma in patients with BE has been shown as an independent risk factor for frequent exacerbation[13], and patients with chronic rhinosinusitis (CRS) report a higher number of exacerbations than those without upper airways involvement[14-18].

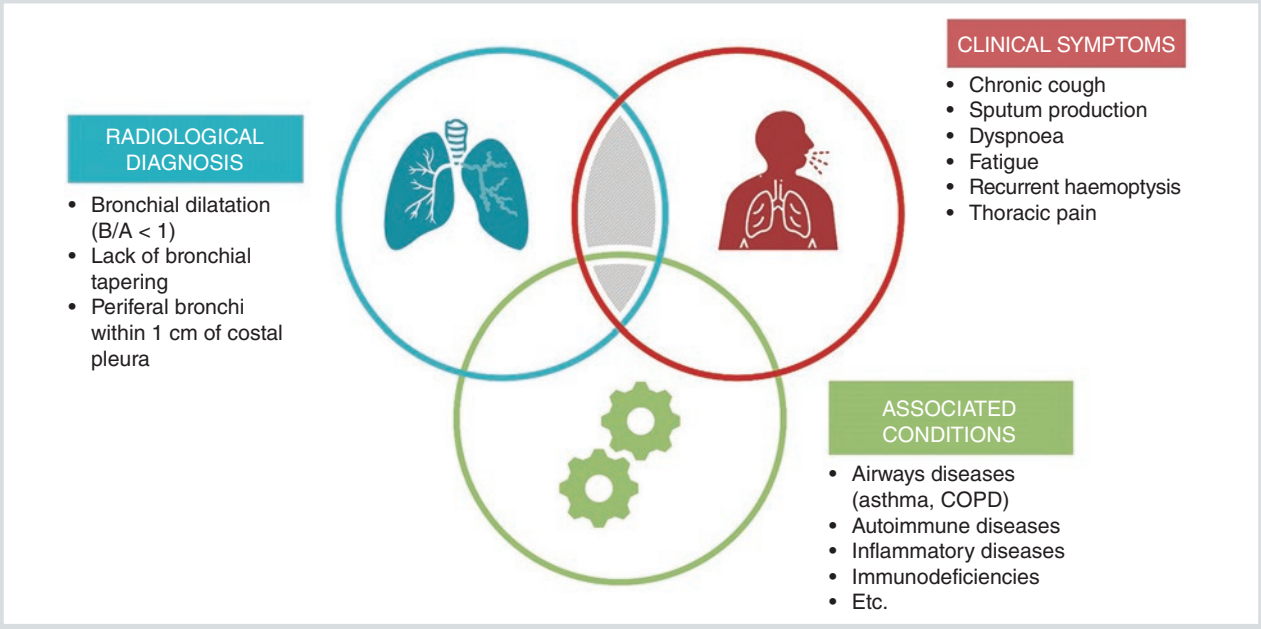

Figure 1. Diagnostic criteria of clinical bronchiectasis. The presence of radiological bronchiectasis and clinical symptoms is mandatory, while other associated conditions can help in the etiological diagnosis but not in defining the disease.
B/A: broncho-arterial ratio; COPD: chronic obstructive pulmonary disease.

Vice-versa, the identification of BE in chronic airways diseases is often a marker of increased severity and worse prognosis. For instance, the presence of BE in COPD patients is associated with more sputum production, more frequent exacerbations, faster decline in lung function, severe airways obstruction, bronchial infection and mortality[7,19-21]. In severe asthma, the presence of BE is associated with older age, non-reversible airflow obstruction, chronic expectoration and more frequent or severe exacerbations[22-24], resulting in increased severity and worse prognosis[25,26].

Likely, the most relevant challenge of these clinical associations is their treatment. For instance, some drugs, commonly used in BE, such as chronic macrolides and nebulized antibiotics[27-29] could be potentially harmful and

Table 1. Derivation of the Bronchiectasis Aetiology Comorbidity Index (BACI) and points allocation

Comorbidity	Points
Metastatic malignancy	12
Haematological malignancy	6
COPD	5
Cognitive impairment	5
Inflammatory bowel disease	4
Liver disease	4
Connective tissue disease	3
Iron deficiency anaemia	3
Diabetes	3
Asthma	3
Pulmonary hypertension	3
Peripheral vascular disease	2
Ischemic heart disease	2

COPD: chronic obstructive pulmonary disease.
Adapted from McDonnell MJ et al.[10] with the author's permission.

contraindicated in presence of other conditions; e.g., the use of inhaled antibiotics is discouraged in patients with asthma due to the increased risk of bronchospasm, while macrolides are not recommended in patients at risk of non-tuberculous mycobacterial (NTM) infection (previous NTM infection, COPD, etc.) to avoid selection of resistant mycobacteria[30-32].

On the other hand, in BE little evidence is available regarding some respiratory mainstay treatments, such as bronchodilators (BD) and inhaled corticosteroids (ICS); in particular, if BD are simply not recommended due to the absence of quality evidence in these patients, data about ICS suggests they could represent a risk factor for bacterial exacerbation[33,34] or NTM infection[32,35].

Moreover, most chronic respiratory diseases usually have an important impact on mental health. The presence of more diseases at once, with increasing symptoms and clinical complexity, can lead to even more frustration and bewilderment in patients. As in the 'Golem legend', sometimes a single world can kill monsters: diagnosing comorbidities in BE patients means giving names to their sources of struggle. A complete diagnosis of comorbidities can contribute to patients' empowerment, by identifying symptoms in the context of a known and recognizable entity, increasing disease comprehension, self-management skills and compliance to treatment[36,37]. Last but not least, in certain countries, an appropriate definition of the main disease and associated conditions can also facilitate reimbursement of medications, access to clinical trials, social services, etc.

In conclusion, identifying respiratory comorbidities in BE patients is crucial for both clinicians and patients, and should be done as soon as possible to avoid delays in treatment (Fig. 2).

In this manuscript, we will review how respiratory comorbidities can be assessed and managed in BE patients trying to keep a practical focus aimed at supporting the clinical decision making in this delicate and complex disease.

ASSESSING COMORBIDITIES OF BRONCHIECTASIS IN A CLINICAL SETTING

The clinical evaluation of BE patients must be very comprehensive since different aetiological or associated conditions can be identified and these findings can have relevant implications for both short- and long-term outcomes.

Clinical presentation

The most frequent and suggestive triad of symptoms includes *chronic cough*, *sputum production* and *dyspnoea*, although *fatigue*, *recurrent haemoptysis* and *thoracic pain* are also quite common[27,38]. However, given the extreme heterogeneity of BE, overlapping and unusual clinical presentations are not rare, making it hard to identify associated respiratory comorbidities and to assess their impact on patients' health. Unfortunately, none of the mentioned symptoms is specific to BE (Fig. 3).

Cough, for example, represents a hallmark of BE syndrome, being reported by > 90% of patients[39], mostly together with sputum production[40]. However, in patients with history of exposure to noxious particles or gases,

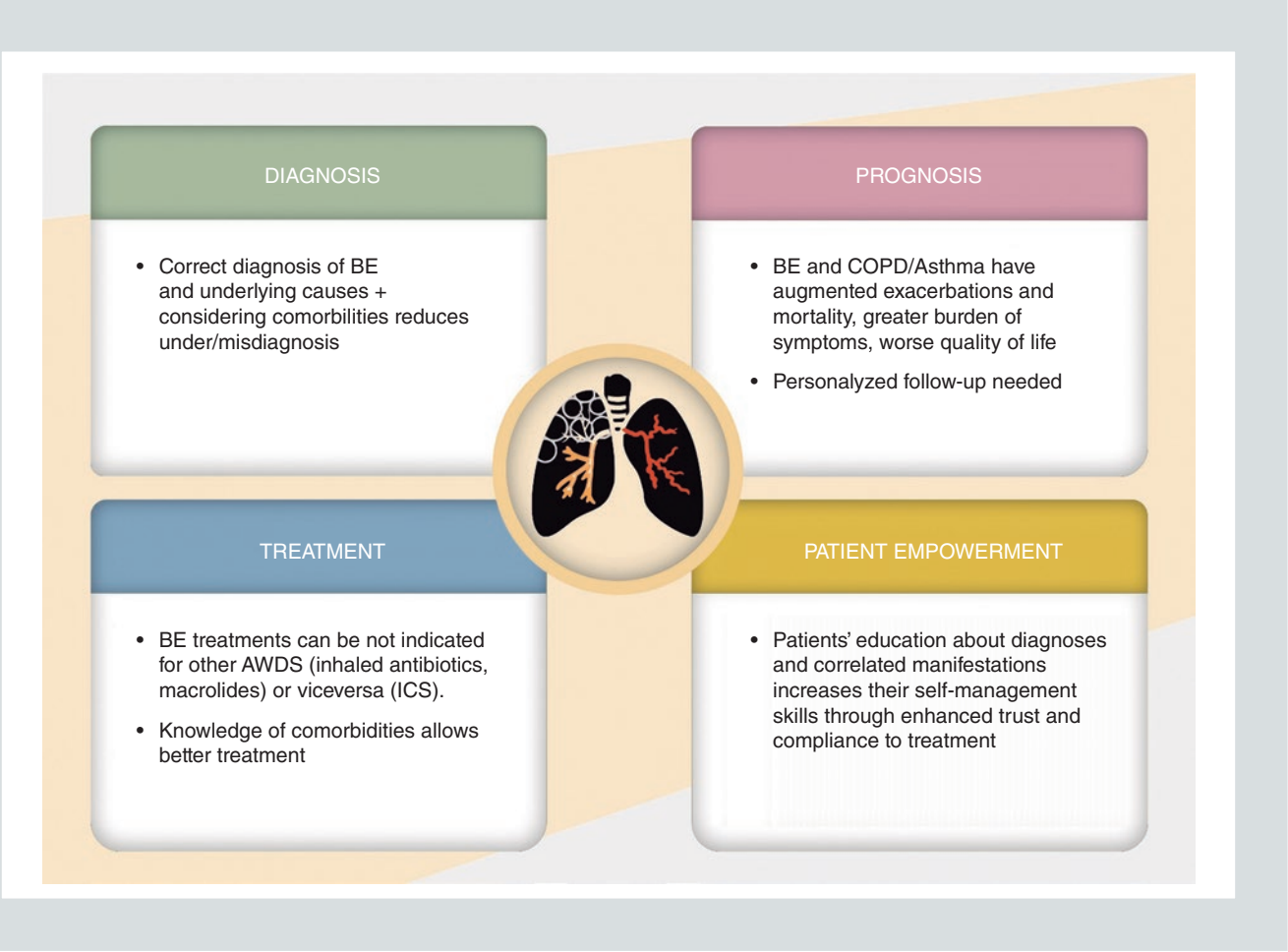

Figure 2. Why should we look for airways comorbidities in BE patients? Considering the effect of comorbidities on prognosis, treatment and patient education, the correct diagnosis of other respiratory diseases improves clinical management of BE patients. AWDs: airways diseases; BE: bronchiectasis; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids.

such as cigarette smoke, toxic fumes, biomasses, etc, the presence of productive cough should always lead to ruling out co-existing COPD[39,41].

On the other hand, *chronic non-productive cough* has been reported only in a small portion of patients with BE, and its presence should raise the suspicion of other respiratory comorbidities such as asthma, upper airway cough syndrome or eosinophilic bronchitis[12,40,42]. Also, persistent or chronic dry cough in pure BE patients should suggest the presence of specific infections, such as NTM disease or allergic bronchopulmonary aspergillosis (ABPA)[43-45].

History of *recurrent respiratory infections* and prolonged time to recovery are commonly reported often since childhood or after a certain episode of airways infection (acute bronchitis, pneumonia, etc.) even in absence of respiratory allergies or toxic exposures. Unfortunately, frequent exacerbations can also be a marker of uncontrolled asthma or COPD and differential diagnosis is required.

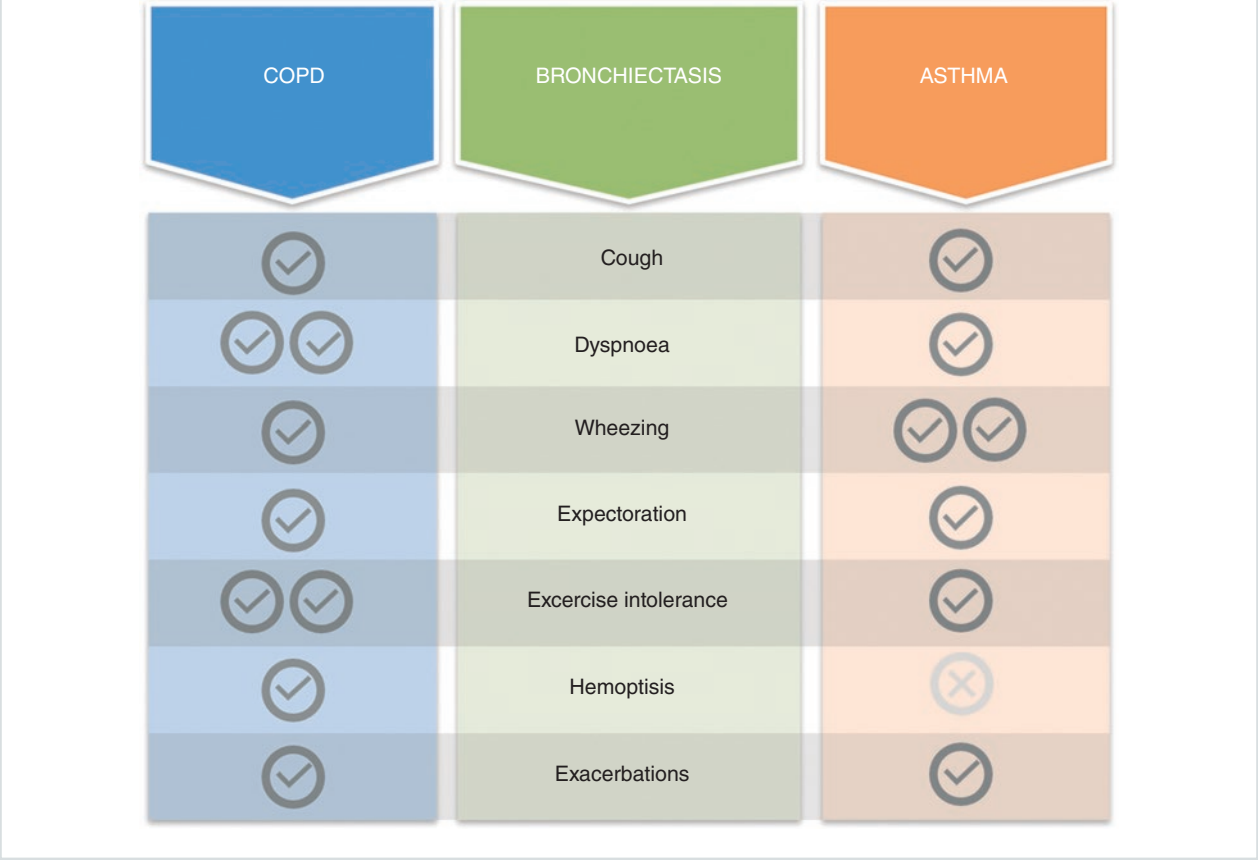

Figure 3. Comparison between most characteristic symptoms of BE, COPD and asthma. Clinical presentation of the three main airways disease can be very similar.
BE: bronchiectasis; COPD: chronic obstructive pulmonary disease.

Despite being quite common in BE exacerbations, *recurrent haemoptysis* should always be investigated, as it could also be related to mycobacterial infection (both tuberculous and NTM), fungal diseases and lung cancer.

Finally, up to 75% of patients with BE may experience *upper airways symptoms*, such as nasal congestion, facial pain and/or anosmia. In presence of these symptoms, the referral to an ear-nose-throat (ENT) specialist might optimize treatment of the associated CRS with or without nasal polyps[11,16,46,47].

Patients with *bronchorrhea and upper airways symptoms* should also be screened for the presence of primary ciliary dyskinesia (PCD), an infrequent but important cause of BE[47].

Lung function tests

In BE, different and non-specific functional patterns can be observed. The obstructive pattern is the most frequent: Radovanovic et al.[48] reported in 2018 that airflow obstruction was found in 41% of their cohort, air trapping in 70%, while only 8% of patients had restrictive

disease. Interestingly, impaired diffusing capacity of the lungs for carbon monoxide (DLCO) was reported in more than half of the population[48]. Recent data suggests that lung function tends to deteriorate over time, especially after exacerbations[49]. However, the pathogenetic mechanisms underlying lung function changes in BE are still poorly understood.

Unlike what happens for other diseases, such as COPD or asthma, lung function tests have little or no diagnostic value in BE, but they need to be included in a wider assessment including imaging, clinical evaluation and patient's personal history. For instance, despite its high prevalence in BE patients, the functional obstructive pattern could suggest co-existing COPD in case of known toxic exposures (tobacco, etc.)[50].

Hyperreactivity can also be observed in BE but it does not necessarily confirm the coexistence of asthma. Unfortunately, a consensus regarding a possible definition of asthma-BE association does not exist at present but likely fluctuating airways responsiveness, history of atopy and wheezing or family history of asthma could be considered in the overall evaluation.

On the other hand, little is known about the restrictive functional pattern in this group of patients. Restriction is known to be a common lung function abnormality in patients with humoral immunodeficiency[51,52], an important cause of BE, but the underlying pathogenic mechanisms of restrictive pattern in BE of any aetiology are unknown. A longitudinal study on 37 patients with common variable immunodeficiency (CVID) showed a fast decline in forced expiratory volume in the first second (FEV_1) loss over time that was associated with increased intravenous immune globulin (IVIG) dose per kilogram, diagnosis of X-Linked Agammaglobulinemia, and younger age at diagnosis[53]. Although these findings have not been further confirmed, it is clear that lung function deserves attention in these fragile patients with BE and immunodeficiency. Nevertheless, the presence of a marked restrictive pattern could also suggest the presence of an interstitial lung disease, such as Usual and Non-specific Interstitial Pneumonia (UIP/NSIP) or sarcoidosis, whose fibrotic changes can lead to traction BE[54-57]. Interstitial lung diseases with traction BE should not be confused with BE disease since they have different pathogenesis, clinical presentation, evolution and prognosis, needing therefore a completely different approach.

Radiology

BE can be defined only and exclusively on the base of a thoracic CT scan. Frequently, BE are diffuse, affecting more than one lobe mono or bilaterally. Despite its crucial role in the initial assessment, the CT scan cannot assess their underlying causes of BE.

However, some radiological findings can suggest underlying or associated diseases[58,59]: middle lobe and lingula, for instance, are the prevalent localization in NTM infection, as testified by the expression "Lady Windermere syndrome" describing female patients with *Mycoce Avium Complex* infection and middle lobar and lingular involvement[59,60]. In PCD, the altered mucociliary clearance leads to mucus stagnation, favouring infection and consequent BE appearance predominantly in the middle and lower lobes[61,62].

Vice versa, bronchial wall inflammation present in ABPA frequently results in the development of central BE involving usually more than one lobe[58,59,63,64].

Beyond extension and localization of BE it is important to check the presence of other well-known radiological findings, such as bronchial wall thickening, air trapping or emphysema, that could suggest the presence of other chronic respiratory diseases[8,65].

Microbiology

Microbes have a leading role in the pathogenesis and natural history of BE: acute and chronic airways infections, especially bacterial, can trigger persistent inflammation, resulting in progressive bronchial damage as historically described by Cole's vicious cycle[66].

Multiple upper airways commensal bacteria can be involved in this mechanism, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*[67]. Indeed, the worst prognosis is usually associated with the chronic infection caused by *Pseudomonas aeruginosa* (PA), a Gram-negative bacterium described in about 25% of BE patients and independently associated with incremented exacerbation, hospitalization and mortality[67-69].

Chronic airways infections are so characteristic and crucial in BE that their presence should be suspected whenever potential pathogen microorganisms (PPM) are repeatedly isolated in the sputum of a patient suffering from any chronic respiratory disease.

Nevertheless, in patients with a primary diagnosis of BE, microbiology is not useful in detecting possible coexistent airways dysfunction or BE aetiologies, with only a few exceptions.

Burkholderia spp, for instance, is classically associated with CF, even if it can sporadically be found also in patients with non-CF BE especially in high-intensity settings as Intensive Care Unit or in presence of immunodeficiencies[70,71].

The isolation of aspergillus species or other fungal pathogens from airways samples is uncommon and clinically not relevant in most cases; nevertheless, it is important to remind the existence of ABPA that is typically characterized by asthma, allergic response to aspergillus and BE. In these cases, a specific assessment of diagnostic criteria is required and analytical follow up is necessary to monitor immunoglobin-E (IgE) levels and response to treatment[44,72].

Inflammatory profiles

Even if the study of airway inflammation is not common in routine, when BE are associated with other airways diseases this kind of investigation can help to understand their complex relationship. In fact, inflammation is a key pathogenic mechanism in all airway diseases, although triggers and cellular and molecular pathways vary considerably (Fig. 4).

In BE, inflammation is mostly neutrophilic, with increased expression of interleukin (IL)-8 and mononuclear cell infiltrates involving CD4+ T cells and CD68+ macrophages[73]. Increase in neutrophil recruitment drives to augmented levels of neutrophil elastase, metalloproteinase

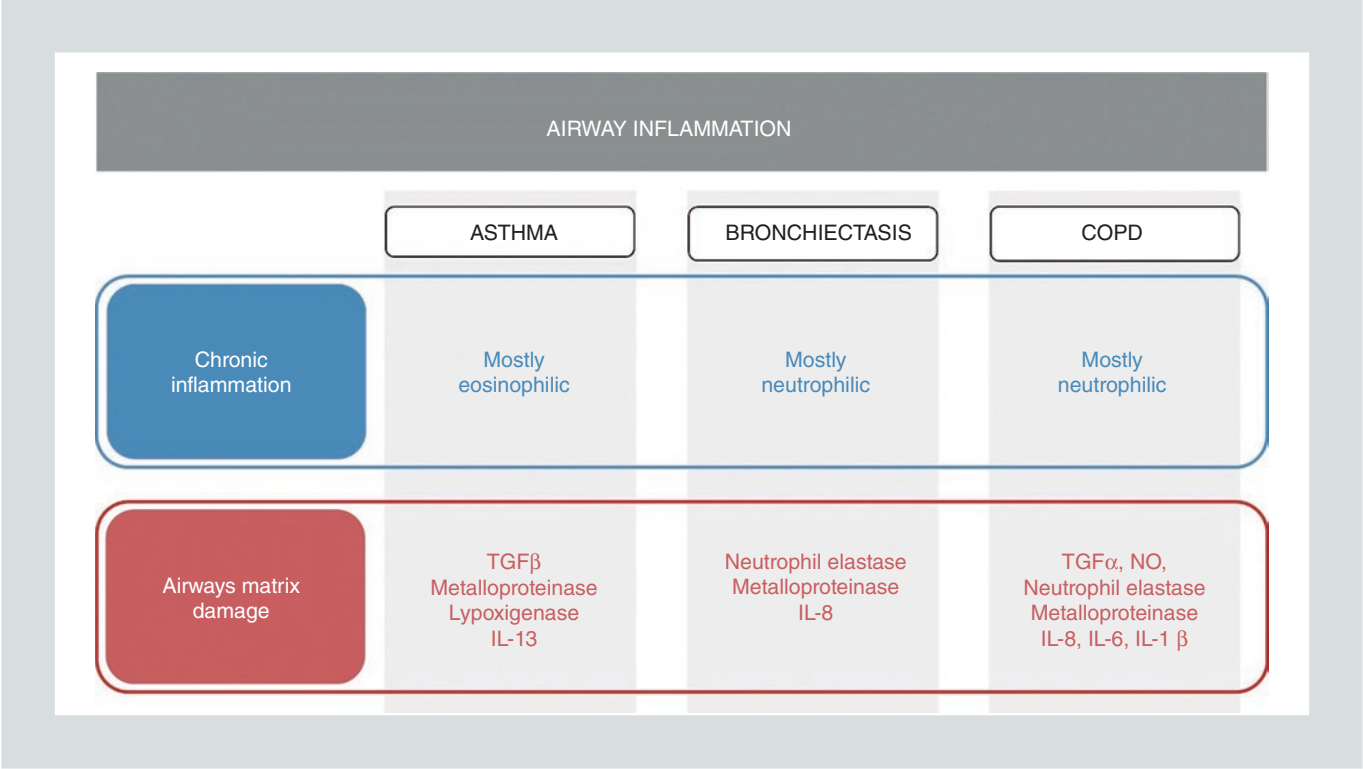

FIGURE 4. Leading inflammatory pathways in BE, asthma and COPD. Despite being all inflammatory diseases and having similar clinical presentations, pathogenetic mechanisms differ considerably between main airways diseases.
NO: nitric oxide. TGFβ: Transforming growth factor beta; TNFα: tumour necrosis factor alpha.

and other proteolytic enzymes, that overcome the action of anti-proteases (like secretory leukocyte proteinases inhibitor [SLPI] and alpha 1 antitrypsin [AAT]), with consequent matrix damage, finally resulting in bronchial deformation[74,75].

In *COPD*, airways inflammation is also mostly represented by neutrophilic/macrophagic insult to bronchial wall and small airways in relation to smoke or other toxic exposure[76]. Typically, bronchial wall is infiltrated by both innate (macrophages/neutrophils) and adaptive inflammatory immune cells (CD4, CD8 and B lymphocytes) that form lymphoid follicles. Smoking activates macrophages to produce a variety of inflammatory mediators including chemokines, reactive oxygen species (ROS) and proteases. Activated neutrophils are a potent source of proteases, particularly neutrophil elastase and ROS. Inflammatory process persists even after smoking cessation based on different potential pathogenic mechanisms, such as autoimmunity (antielastin antibody and T-helper type 1 [T(H)1] responses), altered microbioma and chronic bronchial infections[77].

Differently, the complex inflammatory cascade underlying the development of *asthma* can be resumed in two main pathways, eosinophilic and neutrophilic. The first one, usually involved in allergic asthma, is characterized by a dendritic cell-Th2 cell pattern[78]. The second is characterized by neutrophil activation and Th1/Tc1 and Th17 predominance[79]. Nowadays the new frontiers of respiratory treatment in

asthma are directed at modulating airways and systemic inflammation through different biological therapies blocking specific Ig (see omalizumab etc.) or interleukins, particularly in severe cases with positive results[80].

However, inflammatory pathways of these chronic respiratory diseases are way more complex. In fact, a significant quote of BE and COPD patients can express an eosinophilic pattern of inflammation, with increased levels of IL-13, and also mixed eosinophilic-neutrophilic or paucigranulocitic patterns have been described[81,82].

As a consequence, the study of the inflammation in BE patients is usually not considered crucial in the differential diagnosis of concomitant airways diseases.

Nevertheless, the interest in phlogistic mechanisms underlying respiratory disorders is increasing, as targeting inflammation is proving to be key to their treatment. Therapies directed against neutrophilic or eosinophilic activation are currently being studied both in BE and other chronic respiratory diseases, with encouraging results in specific subgroups of patients. For instance, there are several clinical trials aimed at investigating the role of immune-modulatory molecules addressing neutrophilic maturation/activation or eosinophilic inflammatory pattern in patients with BE[83,84].

In conclusion, although there is still no clear guidance regarding the investigation of airways inflammation to detect respiratory comorbidities in BE, it is likely that in the future new therapeutic options will be available addressing specific biologic phenotypes and personalized management of airways diseases.

CLINICAL MANAGEMENT: PRACTICAL CONSIDERATIONS

Diagnosis, follow up and risk stratification

In the perspective of personalized management of BE, the investigation of potential associated respiratory diseases is necessary. Careful examination of patients' clinical history, signs and symptoms is crucial to direct the rest of the workout and to avoid unnecessary tests. In all patients the diagnostic process of BE should include at least spirometry, high-resolution CT (HRCT) and sputum culture, together with the minimum bundle of recommended aetiological tests (differential blood count, serum immunoglobulins and testing for allergic bronchopulmonary aspergillosis)[27,85].

If a respiratory comorbidity is suspected, further steps must be tailored to the patient according to the clinical suspicion (Fig. 5). Clinical, functional, radiological, and microbiological data should be considered all together in order to frame the disease.

A recent Delphi survey of European experts has described the *association of COPD and BE* as the combination of 1) radiological findings (CT scan), 2) obstructive pattern (spirometry), 3) compatible symptoms and 4) exposure to smoke (≥ 10 pack-years*) or other toxic agents (bio*mass, etc.)[50]. Although the definition has not been validated in clinical cohorts it seems a useful tool to guide clinicians in identification of patients with this frequent association.

In presence of a history of atopy and recurrent bronchospasm, the investigation of hyperresponsiveness, allergies, blood eosinophils

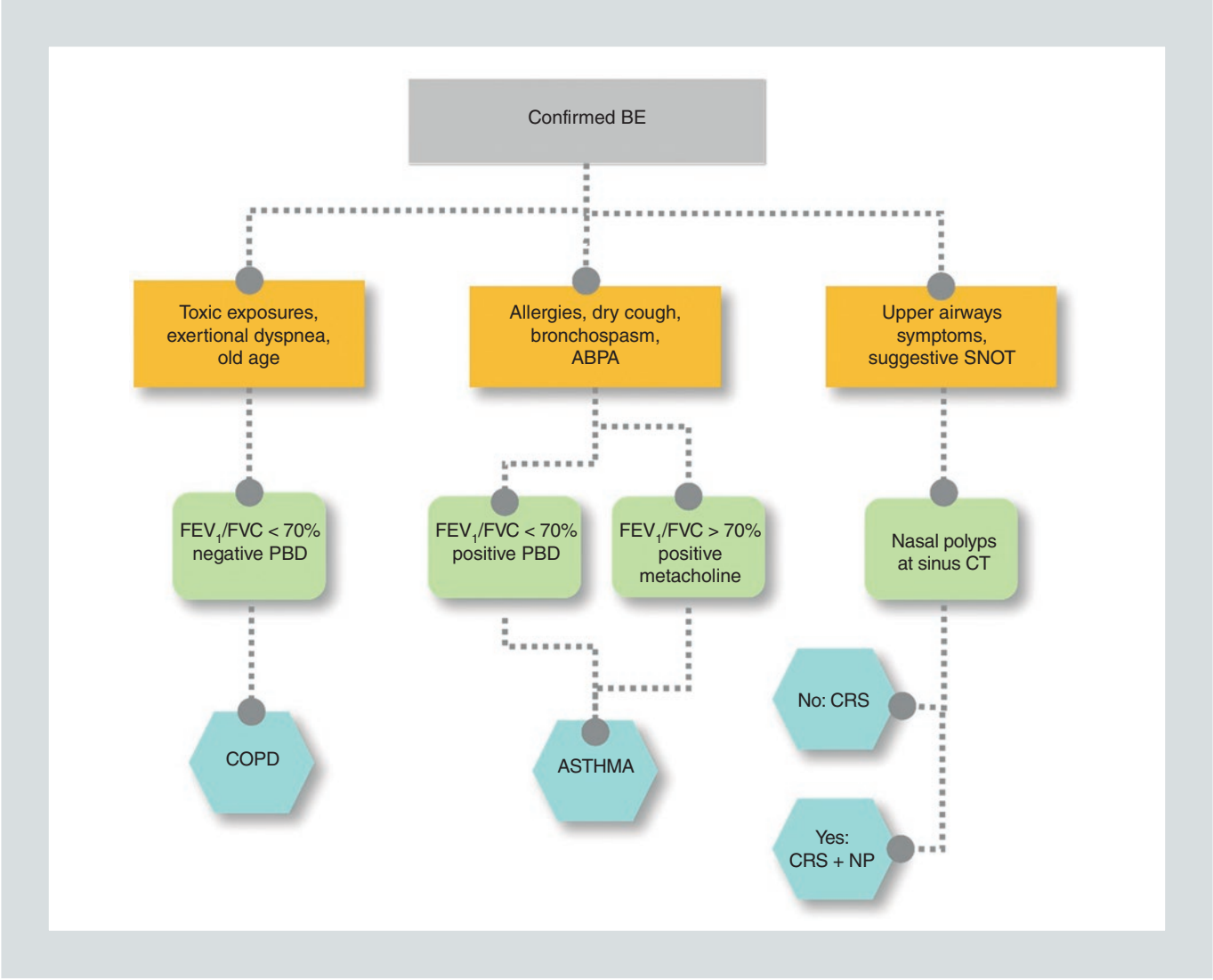

Figure 5. A simplified flowchart to guide in the assessment of respiratory comorbidities in patients with BE.
ABPA: allergic bronchopulmonary aspergillosis; CRS: Chronic rhinosinusitis; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; NP: nasal polyps; PBD: post bronchodilator; SNOT: sinonasal outcome test.

and sputum cell count (airways inflammatory profile) can support the diagnosis of *comorbid asthma* based on usual diagnostic criteria of the Global Initiative for Asthma (GINA) guidelines[86]. Unfortunately, there is no consensus definition about the association of BE and asthma yet, leading though to an empiric approach based on other guidelines.

In presence of clinical suspicion of *chronic rhinosinusitis*, the use of the Sino-Nasal Outcome Test (SNOT) score, a validated, self-administered questionnaire, can help to assess sino-nasal symptoms in BE patients and the eventual need for patient referral to an ear-nose-and-throat specialist. This association is extremely frequent but often misdiagnosed with the consequence of poorly controlled disease in many cases[11].

Additionally, the evaluation of nasal nitric oxide levels can be useful in a preliminary

assessment of upper airways diseases and suspicion of PCD, since a normal or high level has a good negative predictive value[86]. Nevertheless, in presence of doubtful results and high suspicion, a complete study for PCD is recommended, as reported by international guidelines[87,88].

Following the diagnosis, a risk stratification can help to identify high-risk patients and to plan an adequate follow-up schedule. In BE, some tools have been developed to stratify patients according to severity, being the Bronchiectasis Severity Index (BSI) and e-FACED the most used[89,90]. Nevertheless, none of these classifications considers the impact of airways comorbidities, possibly leading to an underestimation of disease severity. For this reason, McDonnell et al.[10] published the Bronchiectasis Aetiology Comorbidity Index (BACI) score that can complement the BSI score in the assessment and prediction of disease outcomes including mortality in BE patients[10]. As shown in table 1, both COPD and asthma are risk factors accounting for increasing risk of worse outcomes.

In presence of these airways comorbidities, it is not fully clear if most exacerbations are secondary to bacterial or viral infections as usually described in BE[78-80,91-94]. In fact, patients with comorbid asthma or COPD could experience exacerbations characterized by increased bronchospasm and dyspnoea but not by purulent expectoration[13]. These factors might clearly influence clinical management and, in particular, pharmacological treatment and outcomes. Again, the absence of clear recommendations for the management of these exacerbation in patients with BE and comorbid asthma or COPD leads to empirical management and, likely, heterogeneous outcomes.

Similarly, in absence of established guidelines, follow-up should be decided on an individual basis but surely prevention of exacerbations and patients' quality of life should be the main objectives of long-term clinical management. Hopefully, more information will come from current studies on biologic phenotypes of BE.

Therapeutical controversies

As mentioned, therapeutical management is particularly challenging in BE patients when respiratory comorbidities are present; in fact, excepting the ROSE definition of COPD-BE association, there is usually no clear definition or guidance for clinical management in the literature. In addition, the literature supporting medical therapy for BE itself is still quite poor due to limited scientific evidence[27] (Fig 6).

For these reasons, we can only discuss the treatments that can additionally be considered in case of respiratory comorbidities of BE and, on the other hand, the drugs whose prescription requires particular attention due to potential limitations or contraindications.

The use of BDs has not been proven to improve clinical outcomes in BE. Nonetheless, their use is empirically recommended for dyspnoea and before inhaled antibiotics and respiratory physiotherapy to improve tolerability and efficacy of these interventions.

When comorbid asthma or COPD are suspected, it is empirically suggested to use BDs in BE aiming at bronchodilatation, airways clearance, and reducing dyspnoea. Unfortunately,

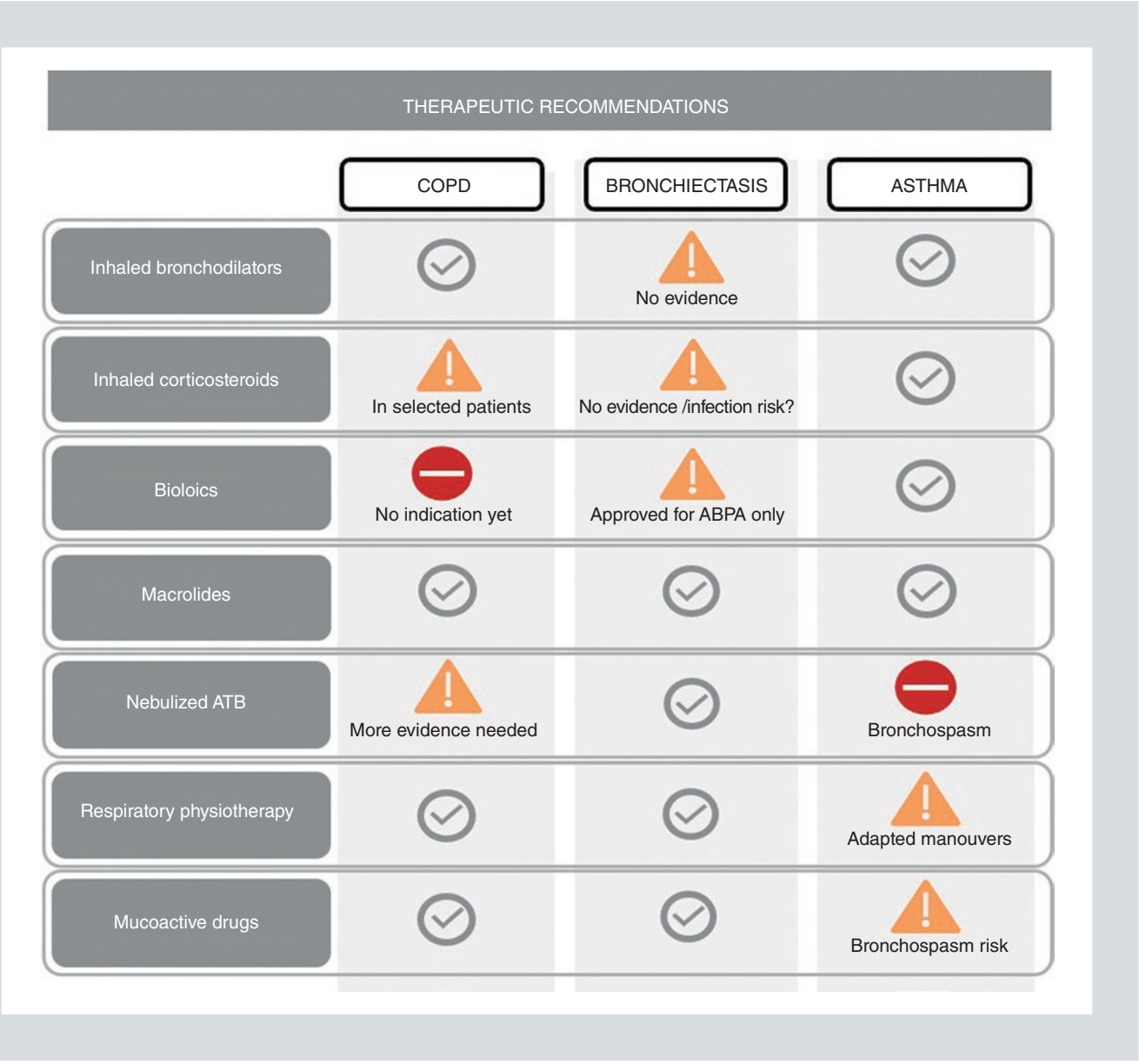

Figure 6. Recommended therapies according to evidences and international guidelines. Indications and guidance about therapeutic management of BE and airways comorbidities is still lacking due to limited scientific evidences. Some treatments require particular attention due to potential limitation and contraindication when used in patients with more than one respiratory disease. Personalized management is recommended..
ATB: antibiotics; ABPA: allergic bronchopulmonary aspergillosis; COPD: chronic obstructive pulmonary disease.

there is no sufficient scientific evidence to assess the clinical benefits of BDs in these cases but until the necessary data is achieved this seems a sensible empiric approach.

Similarly, the use of *ICs* is not supported by solid scientific evidence[34], likely with the exception of clear comorbid eosinophilic asthma, but additional concern regarding their empiric use is based on potential side effects of these immunomodulators. In fact, different kinds of tracheobronchopathy have been described, including infections. In particular, ICs could inhibit bacterial, viral and

fungal airways clearance by blocking macrophage function, inducing apoptosis of dendritic cells, and suppression of T cells activation[95,95]. More specifically, the use of ICs can considerably increase the risk of non-tuberculous mycobacterial infections due to the underlying ecological niche of BE[35]. Therefore, in absence of clear benefits, the use of ICs should be discouraged in patients with BE.

The use of other *biologic anti-inflammatory therapies* is uncommon in BE except for ABPA where omalizumab and other monoclonal antibodies have been successfully used to reduce exacerbations[97]; nevertheless, different trials are currently investigating their use in a specific subset of patients with BE.

Chronic *macrolides* are often used in BE due to their demonstrated effect in improving symptoms, history of exacerbations and quality of life, independently of the aetiology of chronic bronchial infections (*P. aeruginosa* and others). Their use is recommended in BE patients in presence of three or more exacerbations per year. Similar benefits have been demonstrated in both COPD and in persistently symptomatic or uncontrolled asthma patients, irrespective of asthma phenotype[86,99]. Therefore, their use should be safe and beneficial in patients with BE and comorbid asthma or COPD with frequent exacerbations.

In the case of *nebulized antibiotics*, their use has been recommended in BE with the same criteria (three or more exacerbations per year) as macrolides but with a lower level of evidence[27,100,101]. Differently from macrolides, there is no current indication to use chronic inhaled antibiotics in asthma, where the risk of bronchospasm is relevant, or COPD. Nevertheless, recent series have described the successful use of inhaled colistin in severe COPD patients (mean post-BD FEV_1 34-38% of predicted) with chronic bacterial infection by *P. aeruginosa*[102,103]. These retrospective series have shown a significant reduction in the frequency of exacerbations after the initiation of this inhaled antibiotic therapy and an acceptable safety profile at long term. Although no clinical trials have been performed yest, it is likely that in selected patients with BE and COPD, inhaled antibiotics can be used to reduce the impact of chronic infection, particularly *P. aeruginosa*.

Respiratory physiotherapy is usually considered a milestone of long-term treatment of BE but also of COPD; it usually includes a variable combinations of airways clearance techniques, particularly in BE, and rehabilitation programs to reduce exertional dyspnoea, particularly in COPD[27,41,104]. In asthma, physiotherapy can be indicated to improve quality of life (QoL), cardiopulmonary fitness and inspiratory pressure and reduce medication use, but particular care is required to manage bronchospasm by using slow-expiratory airways clearance techniques[105].

Mucoactive drugs can also be helpful in facilitating expectoration and effects of airways clearance techniques in BE but also in COPD where chronic use of acetylcysteine has been associated with reduction in exacerbations[106]. Less evidence is currently available in asthma, but some cases of N-acetylcysteine related bronchospasm have been described[107]. Therefore, in case of bronchial hypersecretion these drugs can be considered but with certain caution in patients with features of asthma.

CONCLUSIONS

The association of BE with other chronic airways diseases is common and associated with worse clinical outcomes. Unfortunately, there is limited guidance regarding their clinical management, but clinical history and additional tests can help in identifying these clinical associations.

During the follow-up of BE patients, careful attention should be given to identify the coexistence of other respiratory diseases. The overlap of different respiratory conditions can increase the complexity of the diagnosis: clinical presentation, lung function and radiology need to be integrated in order to ensure the most accurate diagnosis.

Therapeutic management and follow-up should be based on an individual basis due to the extreme heterogeneity of clinical manifestations, but prevention of exacerbation and patients' QoL should be the main objectives of management. While BDs can be indicated to achieve optimal bronchodilatation and airways clearance, the use of ICs is usually not recommended, with some exceptions. Macrolides can reduce the impact of disease burden in patients with frequent exacerbations, while inhaled antibiotics are crucial in treating chronic bronchial infection, especially from *Pseudomonas aeruginosa*, even if this treatment is not recommended in asthma patients due to the risk of bronchospasm. Respiratory physiotherapy can be recommended but a personalized approach is always required as some patients may require mostly airways clearance intervention while others would benefit from cardio-pulmonary rehabilitation to improve exercise tolerance and reduce dyspnoea.

The complexity of BE and particularly when associated with other respiratory diseases can surely benefit from patient education in order to improve self-management of the disease and reduce the associated psychological burden at long term.

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L. Traversi has nothing to disclose.

A. Alvarez has nothing to disclose.

E. Polverino reports personal fees from Bayer, grants and personal fees from Grifols, and personal fees from Insmed, Chiesi, Menarini, Zambon and Pfizer, outside the submitted work.

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