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Review Article

Bronchiectasis – A Timeless Condition with Recent Developments

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Abstract

Radiologically defined as abnormal and irreversible bronchial dilatations, bronchiectasis are a chronic, progressive respiratory disease clinically characterized by persistent cough and sputum, with a non-negligible impact on quality of life. High-resolution computed tomography of the chest – through the identification of direct and indirect signs – is the gold-standard for its diagnosis.

Marked by heterogeneity in its etiology, evolution and prognosis, bronchiectasis represents the culmination of several factors. Recently, the classical pathophysiological explanation in the form of a cycle has given way to the concept of a vortex, in an unprecedented recognition of the continuous and mutual interrelationship between the various underlying elements.

This review article seeks to define and characterize the concept of bronchiectasis, reflect on the main pathophysiological elements involved, and provide updated data on its diagnostic and therapeutic approach.

Key words: Bronchiectasis, aetiology, pathophysiological vortex, treatable trait.

1.Introduction

Bronchiectasis (BCs) are a chronic and progressive respiratory disease(1) characterized radiologically by abnormal and permanent bronchial dilatation and, clinically, by persistent cough and sputum(2). As a chronic lung disease characterised by such irreversible anatomical changes associated with cough, sputum and recurrent respiratory infections(3, 4, 5), they are the final common pathway of several pathological processes(6).

Identifiable by thoracic high-resolution computed tomography (HRCT)(7, 8) and diagnosed based on imaging and clinical criteria(3, 8), BCs are a chronic inflammatory disease (4) marked by heterogeneity in their etiology, clinical manifestations, radiological appearance, frequency of acute exacerbations (AE), impaired pulmonary function, microbiology and prognosis(3).

In a highly variable and often poorly understood combination, BCs can have numerous causes in their genesis, namely involving processes of infection and inflammation of the airways(7, 8) and different factors that contribute to their progression.

Several aspects of BCs – prevalence, underlying etiology, presentation – vary in different parts of the world(9), but there is a consensus that their incidence and prevalence are increasing globally(10, 11, 12), despite greater infectious control achieved in recent years. This is due to greater diagnostic accuracy, recognition of the association with different systemic diseases, increased population survival, among other factors.

Nevertheless, there has been a change in the epidemiology of the disease, with fewer post- infection cases and more older patients with other prevalent comorbidities, such as Chronic Obstructive Pulmonary Disease (COPD)(13). Thus, they are the 3rd most common disease among airways (after COPD and Asthma)(12), being more frequent with advancing age and among females(5, 14).

2.Clinical and Imaging Presentation

2.1. Clinical Presentation

Although there is no specific patient type due to the heterogeneity of the condition(1), BCs are a clinical syndrome characterized by cough, sputum, and/or recurrent respiratory infections, commonly with progressive development of exertional dyspnea(2, 5).

Complaints of tiredness, episodes of fever, hemoptysis, and thoracalgia may occur daily, intermittently, or only during exacerbations. When the pathological process extends to the upper airways (e.g., cases of Primary Ciliary Dyskinesia [PCD]), complaints consistent with rhinosinusitis and nasal polyposis (NP) may also be frequent(5, 14).

Other clinical features include extrapulmonary manifestations of peripheral muscle weakness (reduced functional capacity for exercise and physical activity), anxiety, depression, decreased exercise tolerance, all of which contribute to impaired quality of life (QOL)(2).

Some patients may be asymptomatic, while others have daily symptoms and frequent AEs(11). Two patients with similar complaints may differ completely in risk factors, comorbidities, lung function, imaging disorders, microbiology, disease severity, lung inflammation, expectations, adherence and social context(1).

Briefly, the cardinal complaints of the disease are:

- Chronic productive cough (most common symptom – 96% of patients);
- Abundant sputum;
- Recurrent respiratory infections;
- Exertional dyspnea;
- Episodes of haemoptoic sputum/haemoptysis in the context of infection(2).

2.2. Radiological Presentation

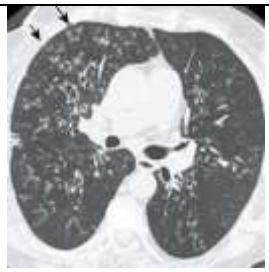
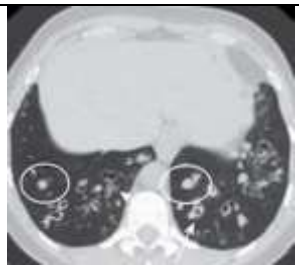
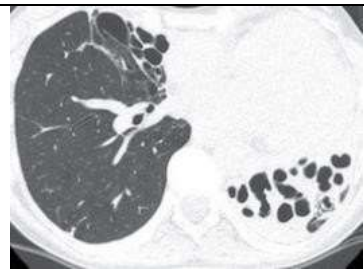
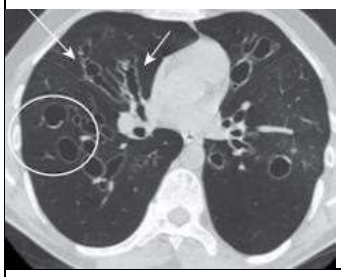
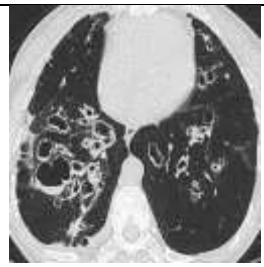
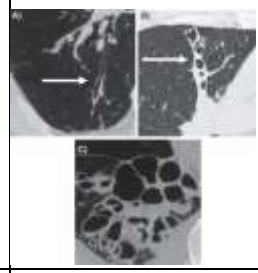
The gold standard test for imaging diagnosis of BCs is the thoracic HRC which, through ≤1mm slices, allows the detection of direct and indirect signs of the disease(14, 15). Direct signs manifest as bronchial dilatation(14) and consist of: 1) bronchial lumen-arterial ratio >1 ("Signet Ring Sign") when the bronchi are perpendicular to the image section; 2) absence of distant bronchial tapering; 3) visibility of peripheral airways ≤1 cm from the costal pleural or in contact with the mediastinal pleura(9, 14, 15). Indirect signs include: bronchial wall thickening, mucoid impaction (with focal opacities, in a "glove finger"), areas of mosaic attenuation (due to air trapping associated with bronchiolar subocclusion due to inflammation/fibrosis), atelectasis, and consolidations(9, 14, 15, 16, 17).

Since a significant percentage of healthy people have discrete BCs in some lung segment(14), imaging findings should always be interpreted in conjunction with clinical practice. Not all radiologically identified BCs are clinically relevant and therefore require treatment(11).

The radiological appearance can be highly influenced by the underlying etiology (e.g., in Cystic Fibrosis [CF] there are usually multilobar BCs with a predominance in the upper lobes, in Allergic Bronchopulmonary Aspergillosis [ABPA] the middle and upper lobes are more affected, among cases of Connective Tissue Disease [CTD], recurrent infections and/or aspiration, the disease predominates in the lower lobes)(9).

Still with regard to the radiological presentation, globally there are 3 morphological types of BCs according to their degree and type of dilation: Cylindrical (tubular; more frequent; bronchi of uniform caliber; due to the absence of normal bronchial tapering in the periphery; signs of the "rail rail" and "signet ring"); Varicose (bronchi dilated and constricted according to an irregular pattern; rosary-like appearance, which may be associated with pulmonary fibrosis) and Cystic (more severe form; dilated bronchi in a blind bottom; possibly with air-fluid levels)(9, 14, 15, 18) – Table 1.

Table 1) Examples of morphological aspects of BCs on Thoracic HRCT scans

		
Tree in bud Sign (arrows)[17]	Sign of mucosal impaction in small Airways (circles) and bronchial wall thickening (arrows)[17]	Cystic BCs in fibroatelectatic areas[17]
		
Varicose (arrows) and cystic (circle) BCs. Loss of millimetric bronchial branching and less visualization of the vascular and bronchial network – air trapping(17)	Cystic BCs(9).	A) Cilindric BCs; B) Varicose BCs; C) Cystic BCs(18).

3. Pathogenesis

Underlying a wide variety of pathological conditions that are not always understood (as discussed below), the pathogenesis of BCs involves key components, namely: impaired mucociliary clearance, bronchial inflammation and infection, and structural changes(8, 19, 20).

Two theoretical models are presented below that aim to reconcile the relative collaboration of each of these elements in the development and perpetuation of the disease.

3.1. Theoretical models:

On the classic explanatory model of this condition developed by Peter Cole – the Vicious Cycle Hypothesis – more holistic views of the problem are now emerging, namely with the replacement of the concept of cycle by that of vortex.

3.1.1. Vicious Cycle Hypothesis:

Historically older, the Vicious Cycle Hypothesis describes the pathogenesis of BCs as a circle of events – dysfunction, inflammation, infection, and structural changes in airways(5, 6). A certain aggressive stimulus, involving any of the aforementioned components, activates a cycle that results in the development and perpetuation of BCs(3).

Varying the "entry point into the cycle" depending on the etiology of BCs(6), this hypothesis considers that the disruption of any of the elements results in disease(8). A succession of events in which each step generates the next, culminating in a persistent and progressive process over time(21).

For example, compromised lung defenses and/or clearance facilitates infection, which in turn triggers a chronic inflammatory reaction and structural changes, further compromising the clearance of AWs, ending the cycle and favoring disease progression(13, 14).

3.1.2. Vicious Vortex Hypothesis:

Considering that the dynamic and mutual interaction between the various key components of the pathophysiology of BCs could not be represented as a circle, emerged the Vicious Vortex hypothesis(1, 6, 21). It presents itself as a more holistic view of the disease, affirming a continuous interrelationship between the key elements, in which all they interact and are influenced by each other, probably to different extents, in different patients or etiologies and at different levels of severity(22).

The concept of Vortex may clarify why treatments alone have only modest effects on clinical outcomes in BCs (21). Targeting only one aspect (e.g., antibiotic therapy for an AE) only blocks one of the disease pathways and is likely to have insufficient clinical results(6, 8, 21). Rather than breaking a vicious cycle (which would be expected to stop the disease), a therapeutic approach directed to a single target will not contain the other elements that perpetuate the problem(21).

The concept of the "vicious vortex" highlights the complexity of the interaction between the various elements involved(6, 23) and advocates a multimodality treatment capable of involving all aspects of the disease(21).

3.2. Key components in the development of bronchiectasis:

As mentioned, there is a consensus among the various explanatory models that there are key aspects in the pathophysiology of the disease – dysfunction of mucociliary clearance, infection of AWs, bronchial inflammation and structural lung injury(1) – which are discussed below.

3.2.1. Impairment of mucociliary clearance:

The term mucociliary clearance includes all the mechanisms by which mucus (composed of water, salt and proteins) and the respective cellular debris, particles and pathogens involved by it, are removed from airways – involving coordinated actions and synchronous movements of the cilia of respiratory epithelial cells(1).

Thus, the correct functioning of the entire system implies a balance between the composition and volume of mucus and periciliary fluid and the frequency and orientation of ciliary beats(24). Mucus and cilia form a "mucociliary escalator" that ensures that foreign agents in airways are transported and swallowed or expelled by cough(25).

In patients with BCs, often exists dysregulation of mucus secretion (with higher amounts of MUC5B mucin), increased osmotic pressure and mucus with a higher percentage of solids (dehydration index) and DNA content(3, 12). These factors change the physical properties of the mucus, with an increase in its viscosity and elasticity and impaired mucociliary clearance(3, 11).

Poor mucociliary clearance can cause sputum retention in airways, leading to chronic infection and inflammation(12, 14).

The mucociliary cleaning process may be impaired by primary cilia dysfunction, secondary to inflammatory injury, or by direct toxicity of bacterial proteins. Some patients have genetic causes for impaired mucociliary clearance (e.g., PCD), but it is usually the combined effects of chronic inflammation and infection of the airways that continually impair this process(10, 26).

3.2.2. Inflammation:

Persistent inflammation is a key aspect of BCs(27), which is not limited to the coexistence of infection, but can be related to dysregulation of the immune response(14). The available evidence suggests an exuberant inflammatory response among patients with BCs – which will be at least partly responsible for lung damage ('collateral damage')(3) and, at the same time, may have important systemic repercussions.

The inflammatory response in BCs is predominantly localized at the pulmonary level, but several studies report elevated levels of systemic inflammatory markers (in phases of stability or exacerbations)(25, 27). Such high levels of pro-inflammatory cells and mediators, oxidative stress and nutritional deficiencies among these patients can have notable systemic repercussions – namely metabolic and/or cardiovascular(20, 28).

Due to the strong relationship with clinical phenotypes and results, knowledge of the associated inflammatory profile may be an important element to subclassify the disease(1).

Recent studies evaluating inflammatory markers and their association with disease heterogeneity have described 3 major categories of inflammation in BCs: Eosinophilic and epithelial inflammation; systemic inflammation; neutrophilic inflammation of airways(11).

In order to promote the control of the underlying inflammatory process (namely with targeted therapy), there is currently an attempt to classify patients into inflammatory endotypes according to their cellular profile – more neutrophilic, eosinophilic or mixed(19).

– Neutrophilic Inflammation:

Neutrophilic inflammation is the dominant inflammatory profile in BCs(1, 6, 12, 19, 27). In response to multiple cytokines and chemokines (Leukotriene B4, Interleukins 8 and 1β, TNF-α), neutrophils are continuously recruited to the AWs, where they perform several functions: bacterial phagocytosis; degranulation and release of proteases and reactive oxygen species (ROS); generation of neutrophil extracellular traps (NETs – i.e., "webs"/networks of DNA and opsonizating proteins of microorganisms that aim to prevent their dissemination and degrade virulence factors), among others(1). However, although they are known to be decisive in immune defence, in excessive amounts, these cells can cause significant tissue damage, particularly with their proteases(14, 19, 22).

In addition, several studies have shown that neutrophils in BCs are dysfunctional(6, 25, 27) – a concept of "Neutrophilic Paradox"(6) –, presenting deficient phagocytosis; excessive activation, degranulation and release of serine proteases (Neutrophil Elastase [NE], Proteinase 3, Cathepsin G) – overcoming anti-protease defense(1, 3, 6); apoptosis long; excessive formation of NETs(9). With regard to the latter, their formation has been strongly associated with the severity of BCs(1, 12).

The function of NETs is to eliminate pathogenic microorganisms but their overproduction leads to tissue injury and persistent inflammation of airways. NETs release neutrophil DNA into AWs with large amounts of enzymes (namely NE)(25). These proteases, antimicrobial proteins, DNA and histones released culminate in excessive inflammation, tissue damage, impaired mucociliary clearance and inability to eliminate pathogens(9).

Regarding NE, several data indicate that it contributes to the production of pro- inflammatory cytokines and mucus, has cilium and cytotoxic properties, and inhibits many innate defenses(14). Studies have shown that patients with BCs often have higher levels of NE in their sputum(6). This serine protease can cleave and inactivate host proteins (including cell receptors involved in eferocytosis, antimicrobial peptides, and extracellular matrix proteins)(1), impair ciliary beat, phagocytosis, and bacterial death, promote extracellular

matrix destruction, mucous gland hyperplasia, and increase mucus production, as well as directly injure airways(8).

Therefore, high levels of NE in the AWs and lungs correlate with early development of BCs(1). Excessive neutrophilic inflammation is related to increased frequency of AE and rapid decline in lung function, namely by degradation of elastin in airways(8). In addition, it is associated with a high bacterial load and loss of lung microbiome diversity(1, 12).

– Eosinophilic Inflammation:

In up to 25% of patients with BCs there is eosinophilic inflammation of the airways contributing to their disease(1, 6) and being able to targeted therapy(19, 27). Eosinophils have bactericidal and antiviral properties against pathogenic microorganisms commonly found BCs(12). Nowadays, eosinophilic inflammation is considered an important factor in the occurrence of BCs unrelated to other diagnoses(1), and has been described in 20-30% of patients with BCs without concomitant asthma(25, 27).

Considering the hypothesis that eosinophilic inflammation could be a driver of BCs pathogenesis and not only a co-factor, in some patients, targeting this pathway could modify the natural history of the disease(27).

– Macrophages:

The number of macrophages in lung biopsies of patients with BCs is increased, although their function is altered(12). These cells are crucial to the immune response against pathogens and to the clearance of apoptotic cells (eferocytosis). Through eferocytosis, they regulate the number of neutrophils in the airways, preventing post-apoptotic necrosis. Impairment in the clearance of necrotic cells promotes the release of inflammatory cytokines, proteases, and ROS, contributing to the persistence of inflammation in airways(6, 12).

Further studies are needed to understand the exact role of macrophages in BCs – in the stability phase and in AE(6).

3.2.3. Bronchial Infection and Microbiome:

Bronchial infection remains a key component in BCs, during AE and in periods of clinical stability(19). It triggers, signalizes, and promotes the inflammatory response, and is one of the main causes for neutrophil migration to the respiratory tract. It creates favorable conditions for the survival of microorganisms – whose persistence results in lesion and abnormal remodeling of airways(1, 14) – and is considered a major factor for disease progression(12).

Infections by bacteria, viruses, fungi or mycobacteria are associated with the development of BCs and with AE of the disease(1). On the other hand, commensal agents may have a beneficial effect on inflammation(19). Thus, the designation of patients chronically infected by pathogens has given way to the notion of microbial dysbiosis – i.e., loss of microbiological diversity, with domination of the microbiome by specific organisms(25).

The development of the microbiome depends on several factors. In the case of the respiratory system, this may include translocation of agents from the upper airways, microaspirations and host defenses, which make heterogeneity a hallmark of the microbiome(6). Its loss – in a process of dysbiosis – can have implications for lung function, inflammatory pattern and disease occurrence.

In BCs, as in other pathological conditions, there is a loss of microbial diversity (with a predominance of small groups of microorganisms)(6, 29). Thus, while the healthy bacterioma of AWs includes Prevotella, Veillonella, Fusobacterium, Streptococcus, Porphyromonas, Neisseria, among others (which reach lower airways through microaspirations of the upper respiratory tract)(25), the organisms that most commonly chronically infect AWs of patients with BCs are Gram-negative pathogens of the Proteobacteria phylum (Pseudomonas aeruginosa [PSAE], Haemophilus influenzae, Moraxella catarrhalis, Enterobacteriaceae) or pathogens from the Firmicutes phylum (Staphylococcus aureus, Streptococcus pneumoniae)(1, 3, 6, 12, 14, 25, 30).

Proteobacterial dysbiome of the microbiome, defined by its dominance (mainly by PSAE and Haemophilus), is associated with more severe disease and worse clinical outcomes(25). In fact, sequencing of the lung microbiome indicated that patients dominated by proteobacteria (PSAE in particular) had more severe disease and that was clearly distinct from that dominated by Firmicutes(1).

PSAE, in particular, is the most identified bacterium worldwide among patients with BCs, being associated with increased frequency of AE, risk of hospitalization and death, and worse QOL. By inducing the formation of NETs, PSAE acquires survival advantage, as these neutrophil "nets/traps" inhibit and eliminate competing microorganisms, and PSAE is able to persist and degrade them, evading inflammatory cells. Patients with PSAE are considered a stable and distinct phenotype, with worse outcomes(2, 25).

3.2.4. Structural changes:

Genetic conditions (such as CF or PCD), congenital malformations, bronchial obstruction, CTD, post-infectious lesions (tuberculosis, pneumonia) can culminate in important structural changes, namely with the development of BCs. On the other hand, in view of the existence of BCs, the overlapping of disease/other

processes can result in the aggravation and progression of structural changes. Examples include the occurrence of infections (e.g., due to the effect of bacterial products on cilia function and cytotoxicity), inflammatory effects (especially with high levels of NE and ineffective NETs), acquired dysfunction of mucociliary clearance due to infection and inflammation.

Regardless of the initial process, BCs are associated with progressive loss of Elastin and Collagen (mediated by Serines, Cysteines, Metalloproteinases) and, therefore, with permanent structural changes(1).

4. Etiology And Diagnostic Approach

As mentioned, BCs are characterized by great heterogeneity in their etiology, form of presentation, and evolution(1). They can result from a variety of conditions – local or systemic, genetic or acquired – but often no one cause is identified(3, 14, 13).

Nevertheless, and given that the specific treatment of a minority of underlying conditions is associated with a better prognosis, in addition to its clinical and imaging diagnosis, BCs require a systematic search for possible underlying etiologies(1, 13).

4.1. Etiological Classification of Bronchiectasis

In order to conduct a sufficiently comprehensive and simultaneously targeted study, it is important to consider the following etiological classification list of BCs (Table 2):

Table 2 – Main etiological groups underlying the development of BCs

Post-infectious	Pulmonary Tuberculosis (PT), Nontuberculous Mycobacterial Lung Disease (NTM), Swyer-James-MacLeod Syndrome, childhood infections (measles, whooping cough)
Immunodeficiency	Primary (e.g., Common Variable Immunodeficiency [CVID]) vs. Secondary (e.g., HIV infection, hematologic malignancy, drugs)
Chronic Respiratory Disease	COPD, Asthma, Alpha1-Antitrypsin Deficiency (DAAT)
Mucociliary clearance defects	PCD, CF, Young's Syndrome, Channel opathies, CF Transmembrane Conductance Regulator-Related Disease (CFTR)
Excessive immune response	ABPA, transplant rejection

Post-inflammatory pneumonitis	Drug inhalation, aspiration, Gastroesophageal Reflux Disease (GERD), Radiation therapy (RT)
Congenital malformation	Mounier-Kuhn Syndrome, Williams-Campbell Syndrome, Pulmonary Sequestration
Connective Tissue Disease	Rheumatoid Arthritis (RA), Sjögren's Syndrome (SS), Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SS), Ankylosing Spondylitis, Recurrent Polychondritis, Marfan Syndrome
Local obstruction	Intrinsic (foreign body, stenosis, neoplasia) vs. Extrinsic (neoplasm, adenopathies)
Other	Yellow Nail Syndrome, Diffuse Panbronchiolitis, Inflammatory Bowel Disease (IBD), Endometriosis, Amyloidosis
Idiopathic	

A. Post-infections BCs:

Infections are the most frequently reported cause of BCs in the literature(12). A post- infectious aetiology of BCs is often assumed when symptoms begin after a severe infection. However, there are cases in which they only appear several years later, when another predisposing factor coexists (e.g., some degree of immunodeficiency). Thus, it is important to ask about respiratory complaints prior to infection, since they may be related to a first exacerbation of a disease that was not previously diagnosed(13). Respiratory infections cause direct structural damage and contribute to the chronic inflammatory process(12). The associated enlargement of peribronchial lymph nodes may result in bronchial obstruction and, secondarily, structural injury(18).

It is widely recognized that sequelae BCs of tuberculosis are associated with more severe disease, greater pulmonary involvement on HRCT-Chest scans, and a predominance of upper lobe affection. Patients generally have a lower body mass index (BMI) and worse lung function(28).

With regard to NTMs, since they are ubiquitous, the development of disease requires some degree of immunodeficiency in the host. Pulmonary involvement is the most common manifestation of the disease and usually progresses. Rarely, hypersensitivity pneumonitis (hot tub lung) may be present. Two major clinical patterns can coexist: older patients with pre- existing structural alterations (BCs and/or cavitations due to previous lung disease); individuals without preexisting pulmonary pathology, usually non-smoking women, with rib cage anomalies and low BMI, who develop nodular, multifocal BCs(13). Lady Windermere Syndrome

occurs with BCs in segments of the middle lobe (ML) or lingula due to infection by Mycobacterium avium intracellulare and often occurs in older women who suppress cough(9).

B. BCs and Immunodeficiencies:

The close relationship between these diagnoses stems from the greater vulnerability to recurrent infections that immunodeficiencies confer(12). Immunodeficiencies are a broad and heterogeneous group of diseases, fortunately of low prevalence, resulting from dysfunction of the immune system. The most prevalent group is relates to deficient antibody production (Acs), which includes immunodeficiencies that present with BCs following recurrent infections: IDCV, specific Acs deficiency, autosomal recessive/X-linked agammaglobulinemia, IgA deficit and Good's Syndrome(13).

CVID is the most prevalent immunodeficiency in adulthood. It presents with clinical infections, recurrent/prolonged diarrhoea and different expressions of autoimmune pathology (AI) and/or lymphoid proliferation. Specific Acs deficiency is much rarer, involving often complicated BCs and recurrent chest infections with normal total Immunoglobulin (Ig) G levels.

Agammaglobulinemia results from a delay in B cell differentiation, culminating in a small amount of these cells and much lower serum Ig levels. Infections develop from about 3-6 months of age (when maternal IgG levels begin to decrease), and immunoglobulin replacement is recommended. IgA deficiency is the most frequent immunodeficiency and tends to be asymptomatic. In view of its diagnosis in patients with BCs, it is important to quantify IgG subclasses and to test specific Acs, since IgA deficiency can progress to CVID/specific Acs deficiency(13).

Finally, Good's Syndrome represents the coexistence of thymoma and immunodeficiency diagnoses and is a rare cause of combined T-cell and B-cell deficiency. Generally identified between the 4th and 5th decades of life, it confers greater susceptibility to bacterial infections with encapsulated, viral and fungal microorganisms. Approximately 75% of patients have BCs, and are associated with more frequent and/or recurrent respiratory infections, pneumonia and inflammatory dysregulation(13).

C. BCs and other chronic respiratory diseases:

BCs can be associated with chronic respiratory diseases – namely bronchial asthma, COPD or ABPA(11). In fact, many patients with BCs have some other respiratory pathology(9), with around 50% of patients with moderate-severe COPD having BCs, and asthma also being one of the most associated comorbidities. Severe

asthma is particularly related to the existence of eosinophilic inflammation and BCs with mucus plugs(12, 25, 29).

– COPD: Similar to what happens among patients with BCs, in COPD the neutrophilic inflammatory pattern tends to predominate(29). The respiratory microbiome includes more proteobacteria, and there is overexpression of pro-inflammatory mucins (MUC5AC) and neutrophil dysregulation pathway proteins(25). As they are associated with increased systemic inflammation, worse lung function and QOL, more sputum and poor prognosis, it is importante to look for the existence of BCs in patients with COPD and very common AE. BCs are usually cylindrical, small, and multiple, dominating in the lung bases(13, 29).

– Bronchial asthma: there is a frequent and clinically significant association between asthma and BCs(29), with BCs estimated to be present in approximately 18-30% of asthmatic patients(13).

Asthma can be considered a comorbidity in patients with BCs, but it is also recognized that the latter can result from the former, particularly in cases of severe asthma. BCs are more common in patients with long-standing asthma, frequent AE and advanced age. Patients with overlap tend to be less atopic and have lower levels of Fractional exhaled nitric oxide (FeNO)(29).

– Alpha-1-Antitripsin Deficiency: as an effective inhibitor of NE, Alpha-1-Antitrypsin (AAT) performs lung protection functions. Therefore, it is recommended to test for DAAT in all patients with BCs(13).

D. BCs and mucociliary clearance defects:

– Primary Ciliary Dyskinesia: PCD is a rare and clinically heterogeneous autosomal recessive genetic disorder characterised by abnormal ultrastructure and/or ciliary function. Ciliary motility impairment results in upper and lower airways disease, with recurrent respiratory infections due to faulty mucociliary clearance(25). The age of presentation is variable, from birth to adulthood. In the neonatal period, it can cause respiratory stress and/or pneumonia without obvious predisposing factors, continuous rhinorrhea from birth, laterality problems or complex congenital heart disease. In childhood/adolescence it tends to manifest itself in the form of chronic productive cough, recurrent respiratory infections, BCs, chronic rhinosinusitis (rarely with NP), otitis media with recurrent effusion, loss of hearing acuity and/or halitosis. In adulthood, NP and halitosis predominate, as well as the occurrence of ectopic pregnancy/subfertility in women and infertility in men (50%)(13, 16).

– Cystic Fibrosis/ other diseases related to Cystic Fibrosis: as an autosomal recessive multisystem disease with several possible phenotypic expressions, most common among caucasians, CF results from mutations in the CFTR gene. Such mutations cause dysfunction of the apical membrane protein CFTR

(regulator of Cl- and Na+ transport in secretory epithelial cells) and consequently result in abnormal ionic concentrations along the apical membranes of these cells. Clinically, it is responsible for the development of diffuse BCs (95%) – often colonized by S. aureus, B. cepacea, etc. –, sinus disease (90-100%), exocrine pancreatic insufficiency (85%; leading to malabsorption), salt loss by sweat glands (100%), male infertility (99%), meconium ileus (20%), distal intestinal obstruction syndrome (20%), CF-related diabetes (20%), liver disease (20%) and NP (10%)(13).

E. BCs and excessive immune response:

– Allergic Bronchopulmonary Aspergillosis: a non-invasive disease caused by hypersensitivity to the ubiquitous fungus Aspergillus fumigatus after inhalation of its spores. It almost only occurs in patients with asthma or CF (2%, 1-15%, respectively). Occasionally, it can complicate other chronic lung diseases, such as idiopathic BCs or those secondary to other causes. Without gender predilection, it is more frequent between the 3rd and 4th decades of life. Most patients report fever, weight loss, severe wheezing and shortness of breath, productive cough with very thick sputum, and sometimes dark brown mucus plugs(13). They are, essentially, central BCs, whose development is believed to be secondary to the impaction of mucous plugs in the bronchial walls previously weakened by eosinophilic infiltration(31-33).

F. BCs and Post-inflammatory Pneumonitis:

Post-inflammatory BCs may develop after acute inhalation injury or be related to chronic aspiration and severe GERD(12).

– Gastroesophageal Reflux Disease: frequent comorbidity (26-75% of patients with BCs). It is believed to contribute to BCs by 2 major mechanisms: vagally mediated bronchoconstriction reflex and pulmonary microaspirations(25). The existence of a causal relationship between GERD and BCs is controversial, but it is known that GERD can negatively impact BCs(13).

H. BCs and Connective Tissue Disease: BCs are a frequent extra-articular feature of RA (prevalence ~20%)(25), and are associated with rapidly progressive disease and frequent AE(12). In SS, the prevalence varies between 7 and 54%. They are usually older patients, with hiatal hernia, higher frequency of anti-smooth muscle and anti-SSA Acs(25).

J. Other causes of BCs:

– Inflammatory Bowel Disease: pathogenic mechanisms are poorly understood, and there is the theory of the "Lung-Gut Axis" which, by affirming a common derivation of the embryonic cell line, argues that the same inflammatory process occurs at the pulmonary and intestinal levels in certain patients(25).

– Diffuse Panbronchiolitis: idiopathic inflammatory disease that mainly affects the respiratory bronchioles, causing severe suppurative obstructive pathology. More common among Asians and with 2/3 of patients being non-smokers, clinically present with productive cough, profuse sputum, exertional dyspnoea and chronic sinusitis(13).

4.2. Diagnostic approach:

In view of the above, if there is suspicion/identification of BCs, the following diagnostic approach is recommended:

i. Clinical History and Objective Examination;

ii. HRCT Thorax;

iii. Baseline laboratory study;

iv. Additional laboratory study;

v. Other studies.

i. Clinical History and Objective Examination:

The clinical approach should begin with a clinical history capable of detailing and contextualizing respiratory and other symptoms (age of onset, presentation and clinical evolution, therapies), pre-existing diseases, inhalational/other risk exposures, family history (including consanguinity) and/or infertility(13). The approach of comorbidities and previous medical history, with identification and characterization of potentially responsible/contributing conditions (e.g., RA, COPD, Asthma, GERD, etc.), is therefore particularly important throughout the diagnostic process(16) (Table 3).

Table 3 – Clinical features and possible etiology of BCs(13,14)

Clinical presentation	Possible etiology
Age of symptom onset - Neonatal period - Childhood - Adulthood (> 40 years) - Elderly women	 - PCD, CF - CF - Idiopathic BCs - MNT
Chronic symptoms from the onset	- Idiopathic BCs
Smoking and/or occupational exposures	- COPD - Toxic Inhalation - MNT
History of infection	Measles, whooping cough, pneumonia, PT
Chronic sinusitis	- PCD, CF, Young's Syndrome; - Diffuse panbronchiolitis; - Yellow Nail Syndrome; - Idiopathic BCs.
Nasal Polyposis	CF; Asthma
Recurrent otitis media; Hypoacusis	PCD
Sub/infertility	PCD, CF, CFTR-related disease, Young's Syndrome
Susceptibility to infections	Immunodeficiencies (primary/secondary)
Gastrointestinal symptoms - Diarrhoea - Symptoms of malabsorption - Recurrent chronic/acute pancreatitis - Pyrosis	 - IBD - CF - CF/ CFTR-related disease - GERD
Gastric banding	Aspiration
Previously diagnosed diseases	COPD, Asthma, TDC/ AI disease, IBD
Severa asthma	ABPA
Family history (Genetics/ Inbreeding)	- PCD, CF - Primary Immunodeficiencies
Characteristics of sputum - **Scarce** - **Brownish corks** - **Purulent, abundant and without microbiological isolations**	 - Bronchiectatic/nodular NTM disease - ABPA - IBD
Ethnic origin	Diffuse panbronchiolitis

Similarly, in addition to a systematized evaluation by systems, it is important to look for specific stigmas of CTD, IBD, consumption and other conditions(3, 5) on the Objetive exam.

ii. HRCT Chest:

A fundamental element in the diagnosis of BCs, HRCT is also of paramount importance in the evaluation of the severity of the disease, which is related to the imaging extent (i.e., the greater the number of lung lobes affected, the more severe the disease)(15).

BCs can be localized or generalized (most commonly, especially at the level of the lower lobes)(18), and HRCT scans also allow a relationship between their distribution and possible underlying pathophysiological processes (Table 4).

Table 4. Imaging distribution of BCs on HRCT-Chest scans and potential etiology

Localized BCs	- Sequelae of PT; - Intrinsic bronchial obstruction; - Extrinsic bronchial obstruction.	
Diffuse BCs	**Central Distribution**	**Peripheral distribution**
	- ABPA; - *S. Williams-Campbell*; - *S. Mounier- Kuhn*.	Upper lobes: CF; sequelae of PD; Middle Lobe and Lingula: NTM; DCP; Lower lobes: Idiopathic BQ, Immunodeficiencies, COPD.

iii. Baseline laboratory study:

Despite the lack of standardized tests globally accepted by the various scientific societies as an initial laboratory study for the diagnosis of BCs, most of the available literature suggests the following as minimum tests:

- Differential celullar blood count;
- Protein electrophoresis;
- Determination of serum Igs (IgG, IgA, IgM);
- Tests for ABPA (total IgE, IgE and IgG specific for Aspergillus, Eosinophils);
- Serum AAT determination;
- Microbiological examination of sputum(3, 5, 12, 14, 16).

iv. Additional laboratory study:

Depending on the characteristics of each patient and their particular clinical context, a selected set of studies should then be carried out with a view to excluding the main known etiologies of BCs. For example, it is important to review a diagnosis of idiopathic BCs in the face of marked clinical deterioration or age ≤50 years(16).

In the case of suspected NTM lung disease and absence of sputum, bronchoscopy with bronchial lavage may be important. Similarly, in localized BCs, bronchoscopy will help in the identification/exclusion of potential endobronchial lesions/foreign bodies as a cause of BCs(16).

In the presence of clinical suggestion of Immunodeficiency (primary and/or acquired), it will be useful, after serum determination of Igs, to proceed to the study of the vaccine response to Pneumococcal and Tetanus immunization, with or without the development of specific Acs(15), as well as the determination of serum titers of IgG subclasses and the study of the main lymphocyte subpopulations in peripheral blood (T cells-CD3 subpopulations, CD4, CD8, B and NK cells)(13). At the same time, it is important to look for acquired forms of immunodeficiency, namely by screening for HIV infection and Hepatitis B and C.

After verification of DAAT by serum determination, genetic study and immunophenotyping should be carried out(15).

If PCD is suspected, screening for the disease should initially be performed (with nasal Nitric Oxide [NO] measurement) and, if positive, confirmatory testing demonstrating abnormal ciliary structure and/or function will be required. Tests should be done in a period of stability (i.e., ≥4- 6 weeks prior to measurements)(13).

Nasal levels of NO have a specificity of 96% and sensitivity of 91%(3). Confirmatory tests may involve high-speed electron and video microscopy, immunofluorescence, or genetic testing(16) (Table 5).

Table 5. DCP Screening and Diagnostic Tests[13].

Screening test	**Nasal Nitric Oxide**	Low nasal ON has high sensitivity and specificity after exclusion of CF in adults and children aged ≥5 years. Normal/elevated nasal ON may be considered to exclude PCD.
Diagnostic test	- **Analysis of ciliary structure:** electron microscopy; - **Ciliary function analysis:** frequency and pattern of ciliary movements through video analysis.	-Biopsy; Brushed/biopsied with nasal/bronchial forceps. - If not conclusive, repeat analysis.

Other test	**Genetic testing**	Genetic causes of 1/3 of PCD cases remain unexplained

All children with BCs should be studied to exclude CF. Similarly, in adults with suggestive features (gastrointestinal malabsorption, male infertility, history of steatorrhea in childhood, persistent isolation of S. aureus in sputum, BCs of the upper lobes, pancreatitis, etc.) the possibility of CF should be considered(5, 13, 16).

Initially, two measurements of Cl- in sweat should be performed (quantitative test) and, in case of altered values, mutations in the CFTR gene should be analysed(13).

As mentioned above, ABPA is also a possible cause of BCs. Therefore, sensitization to A. fumigatus should be evaluated in all patients with BCs (specific IgE and IgG or Skin Sensitivity Tests [TSC]). Recently, diagnosis of asthma ou CF, elevated serum total IgE (>1000 IU/mL) and increased specific IgE or TSC for Aspergillus have been proposed as major/mandatory criteria for the diagnosis. The minor criteria were: serum precipitins/IgG for A. fumigatus, peripheral eosinophilia (>500-1000 cells/L) in patients naïve for corticosteroids, and radiological findings consistent with ABPA (transient [consolidations, centrilobular nodules, glove-finger opacities] or permanent [varicose/central cystic BCs, pleuropulmonary fibrosis])(13).

If clinically compatible, investigate possible GERD and frequent aspirations(16).

In the event of changes/complaints consistent with arthritis, CTD and/or systemic vasculitis, determine Rheumatoid Factor (RF), Anti-Cyclic Citrulline Peptide (Anti-CCP), Antinuclear (ANA) and Anti-Neutrophil Cytoplasm (ANCA) Acs, as well as additional AI study guided by the suspicion in question(16).

vi. Other studies:

– Pulmonary Function Tests (PFT): no less important and transversal to all patients, PFT should be performed. An obstructive (mild to moderate) ventilatory pattern often predominates, followed by progressive functional decline over time. It is considered that obstruction is mainly related to the involvement of small and medium-sized airways(18).

The functional study should include spirometry with bronchodilation test, plethysmography, and determination of the diffusing capacity of carbon monoxide (DLCO). Additional studies (e.g. with arterial blood gas analysis [GSA], Six-Minute Gait Test [PM6M] and/or Cardiorespiratory Exercise Test [PECR]) should be considered on a case-by-case basis.

– Prognostic Scores:

BCs represents a condition with an unpredictable clinical course, which tends to progress slowly, but can have a rapid evolution(18). The main causes of mortality in BCs are respiratory failure and respiratory infections(9). The severity and prognosis of the disease vary among individuals, leading to the need for prognostication and phenotyping(12).

This process is facilitated by the application of scales/scores validated for this purpose, namely: BSI (Bronchiectasis Severity Index), FACED and BACI (Bronchiectasis Aetiology Comorbidity Index). BSI is more complex but also more accurate than FACED. The BACI includes 13 comorbidities potentially associated with outcomes and mortality in BCs(12).

- BSI: through the pontuation in 9 variables (age, BMI, Forced Expiratory Volume in the 1st second [FEV1], hospitalizations in the previous 2 years, number of AE in the last year, dyspnea [according to modified Medical Research Council scale [mMRC], colonization by PSAE or other microorganisms, radiological severity) identifies independent risk factors for mortality, AE, hospitalizations, and impairment of QOL. Therefore, it considers clinical, radiological and microbiological parameters(9) and classifies the disease into 3 grades: mild (0-4 points), moderate (5-8) or severe (9-26), which are associated with different rates of mortality and hospitalization(12, 14, 31).
- FACED: evaluates functional, physiological, microbiological, radiological and clinical parameters(31) using 5 variables (FEV1, age, PSAE colonization, radiological extension and dyspnea [mMRC scale]) and classifies patients according to risk of mortality in 5 years (9, 12, 14, 31). All variables range up to 7 points, distinguishing groups of patients with mild (0-2 points), moderate (3-4) and severe (5-7) BCs. The E-FACED score is a modified version, in which 2 additional points are assigned if AE in the prior year required hospitalization(12).
- BACI: evaluates the impact of comorbidities on the risk of hospitalization and mortality at 5 years in patients with BCs(14).

5. Therapeutic Approach

In order to prevent AE, relieve symptoms, improve QOL, and delay disease progression(3, 12, 14,23), the therapeutic approach to BCs should include (whenever possible) treatment of specific identified causes and a combined action on the various elements of the pathophysiological vortex of the disease(3, 14). Thus, in

addition to general measures and adequate management and prevention of complications(1, 11), it will be necessary to promote mucociliary clearance, to act on bronchial infection and inflammation, and know how to manage complications resulting from existing structural changes.

5.1. Treatment of specific causes:

Although the infrequency with which a specific cause of BCs is identified, its in-depth study should always be encouraged, namely by the existence of therapeutic options capable of reducing the progression of the disease in particular cases – as is shown in Table 6 (24)

Table 6 – Examples of specific causes of BCs and their targeted treatment

BCs causes	Specific treatment
Acs production deficit	EV/SC immunoglobulins
ABPA	Oral corticosteroid therapy and antifungals
DAAT	- Smoking cessation and avoidance of other risk inhalation exposures; - AAT replacement in PiZZ phenotypes, rare deficient variants, and some SZ with serum AAT <57mg/dL, pulmonary emphysema, and FEV1 <80%.
DRGE	Proton Pump Inhibitor
MNT Infection	Second microorganism involved and current guidelines
Associated comorbidities (COPD, Asthma, BD...)	Treatment of the condition involved
Bronchial obstruction	Surgery/ Endoscopic bronchial dilation
CF	CFTR modulators, DNAse

5.2. General measures:

Nutritional assessment is one of the key elements in the approach to patients with BCs, as BMI is an independent marker of survival – with malnutrition being associated with more complications and a higher risk of mortality(24).

Likewise, prevention of respiratory infections (flu, pneumococcal, anti-SARS-CoV-2 vaccination), smoking cessation and treatment of complications (respiratory failure, hemoptysis, among others) are transversal pillars for the various patients(14).

5.3. Promotion of Mucociliary Clearance:

In order to achieve adequate mucociliary clearance, and depending on the particularities of each patient, it will be important to use mucolytics, hyperosmolar agents and physiotherapy/respiratory rehabilitation (RR)(9).

– Mucolytic agents: they reduce the viscosity of bronchial secretions and thus facilitate their drainage. Particularly indicated for patients with difficulty in releasing sputum, they can reduce the number of AE(15, 24). Examples are: Acetylcysteine, Carbocysteine, Erdosteine, Bromhexine. Acetylcysteine dissociates mucin disulfide bonds, reducing the viscosity of mucus. It has anti- inflammatory and antioxidant effects (reduces ROS and inflammatory mediators in airways) and limits bacterial adhesion to epithelial cells. Carbocysteine increases the sialomucin content of mucus, reduces inflammatory cytokines, and decreases the influx of neutrophils into airways
(12). Erdostein, on the other hand, has antitussive and antioxidant effects(12), reduces sputum purulence and improves spirometric parameters(14, 24). Bromhexine reduces the volume of secretions and facilitates their elimination(24), while dornase-alpha is only indicated in CF(14, 16).

– Hyperosmolar agents: promote hydration and increase the osmolarity of the surface fluid of the airways, through the influx of water and reduction of viscoelastic properties of the mucus. Before using a hypertonic substance, a tolerance test should be performed by means of forced spirometry before and after inhalation, and the hyperosmolar agent should be discontinued if it causes a reduction in FEV1 ≥15%(24).
Mannitol is a poorly absorbed monosaccharide that, when administered as a dry powder,
promotes the influx of water into the lumen of airways(12). Approved for patients with BCs aged
≥18 years, it can improve QOL and increase time to first AE(24). Nebulised hypertonic saline is a cost-effective and generally well-tolerated option that also influences the physical properties of mucus, particularly when used with other airways clearance strategies(3). Particularly interesting for patients with sputum volume >10mL/day or ≥2 AE/year(15).

– Respiratory Rehabilitation: in order to improve their ventilatory capacity and exercise tolerance, reduce dyspnea and improve QOL, it is recommended that patients with BCs and functional limitations resulting from them join a RR program. Data show that RR, including secretion drainage techniques and exercise training, with a frequency of 3 sessions/week and for ≥8 weeks, reduces the frequency of AE among these patients(15), and that it is crucial that they learn and perform them regularly(5).

– Techniques for airways cleaning: of widely recognized importance, it is essential to teach and integrate techniques for airways cleaning in patients with BCs(2), namely by enabling them to perform them one or more times a day(5). Involving the creation of mechanical stress(26), such techniques seek to prevent mucosal stasis and lung obstruction and injury resulting from them(5). There are several possibilities – active and/or passive (performed by another person), manual and/or instrumental (14) –, namely positional options (postural drainage), expiratory flow modulation techniques (active breathing cycle techniques, autogenic drainage,

forced expiratory techniques), percussion, vibration and chest compression, actions with positive pressure devices (oscillatory and non-oscillatory – Flutter, Acapella, Aerobika, Affovest)(2, 12, 15, 16). Active cycle breathing techniques (ACT) increase the volume of sputum with a view to its release and reduce the impact of coughing(5). They are safe, QOL-enhancing, and recommended in patients with clinically stable BCs with productive cough(3, 24). Ideally included in a global training program (≥1x/day), they can be manual (autogenic drainage, slow exhalation with open-cycle ventilatory techniques and active glottis – reducing pulmonary hyperinflation) or instrumental (positive expiratory pressure [PEP], positive expiratory oscillation [OPEC], high-frequency extrathoracic oscillation)(24).

Various instruments can be combined with ACTs, namely mechanical in/exsuflation (e.g., CoughAssist), high-frequency chest oscillation devices (e.g., Vest), positive expiratory pressure devices (e.g., Threshold), and OPEC instruments (e.g., Acapella, Aerobika, Flutter)(12). They can achieve a higher expiratory-inspiratory flow rate or direct air volume to regions obstructed by mucus accumulation(26).

To improve the drainage of secretions, short-acting β-adrenergic agonists (salbutamol, terbutaline) should be administered prior to respiratory physiotherapy(24).

– Exercise training and muscle strengthening: RR programs for patients with BCs are carried out in multiple contexts (hospital, outpatient, home-based, telerehabilitation), and exercise prescription should be adapted on a case-by-case basis. Generally, moderate-high intensity resistance training(2), upper and lower limb muscles (progressive load, starting at 60% of maximum load) and inspiratory muscles are recommended(24).

5.4. Action on Bronchial Infection:

As previously mentioned, bronchial infection has long been considered central to the pathophysiological vortex of BCs, and it finds antibiotic therapy as a cornerstone of its approach. Thus, antibiotic therapy is considered to have 3 major indications in this context: eradication of newly identified pathogenic microorganisms (i.e., promotion of sustained cultural conversion), long-term maintenance therapy, and treatment of EA(12).

For further clarification, it is important to differentiate the concepts of initial, intermittent and chronic bronchial infection, as well as acute exacerbation of BCs (Table 7).

Table 7 – Definition of the concepts of initial, intermittent and chronic bronchial infection	
Initial bronchial infection	First isolation of a microorganism (14, 15).
Intermittent bronchial infection	Intermittent isolation of the same microorganism in cultures separated by ≥1 month. Positive and negative cultures for 1 same agent in consecutive specimens separated by ≥1 month after initial infection (14, 15).
Chronic bronchial infection	≥2 positive respiratory cultures for the same agent with an interval ≥3 months, for 1 year. Cultures persistently positive for a microorganism (14, 12).
Acute exacerbation of BCs	Episode of clinical worsening beyond the usual daily variation, lasting ≥48 hours and implying therapeutic alteration. It usually involves ≥3 of the following: cough, increased volume and/or purulence of sputum, accentuation of dyspnoea, fatigue and/or haemoptysis (2, 11, 14).

– Approach of an initial bronchial infection:

After initial identification of PSAE, eradication should be attempted(24). The European Respiratory Society (ERS) guidelines recommend eradication antibiotic therapy for adults with BCs and a new isolation of PSAE with 3 possible protocols and a total duration of 3 months:

• Oral fluoroquinolone for 2 weeks, followed by intravenous (IV) antibiotic therapy (β- lactam and aminoglycoside) and inhaled (colistin, tobramycin or gentamicin);

• Sequential treatment with 2 weeks of IV antibiotic therapy (β-lactam and aminoglycoside) followed by inhaled antibiotic therapy;

• Combination treatment for 2 weeks (oral fluoroquinolone/IV antibiotic therapy and inhaled antibiotic), followed by maintenance of inhaled antibiotic therapy(12, 24).

Eradication may also be advised in the initial methicillin-resistant Staphylococcus aureus (MRSA) infection, namely with Co-trimoxazole and Rifampicin (over 2 weeks) or by combining several oral antibiotics (Fusidic Acid, Co-trimoxazole, Clindamycin, Linezolid), with/without inhaled Vancomycin(12).

– Approach of a chronic bronchial infection:

Although it is not the case for all microorganisms, with regard to chronic bronchial infection by PSAE, there is a consensus that its eradication is indicated, as already mentioned. Chronic PSAE infection is associated with a worse prognosis, a higher rate of AE, deterioration of QOL, and increased mortality(3, 14).

With regard to the other agents, it is known that the occurrence of ≥3 AE/year doubles the risk of mortality, so this is the most commonly used criterion to recommend the approach to chronic infection with the administration of continuous antibiotic therapy (2, 4, 12, 14, 16, 24). On average, they occur 1-2/year. The main risk factors for AE are greater radiological extension, worse prognostic scores, history of recurrent AE in the last year, chronic bacterial infection, malnutrition, and other harmful socioeconomic factors(14).

In this context, and as illustrated in diagram 1, macrolides constitute the most effective antibiotic class, reducing AE by 50%(1). Azithromycin (250-500mg, 3 days a week,) for 6 to 12 months may be the option of choice(15).

Diagram 1 – ERS recommendations for addressing chronic infection in patients with ≥3 AE/year

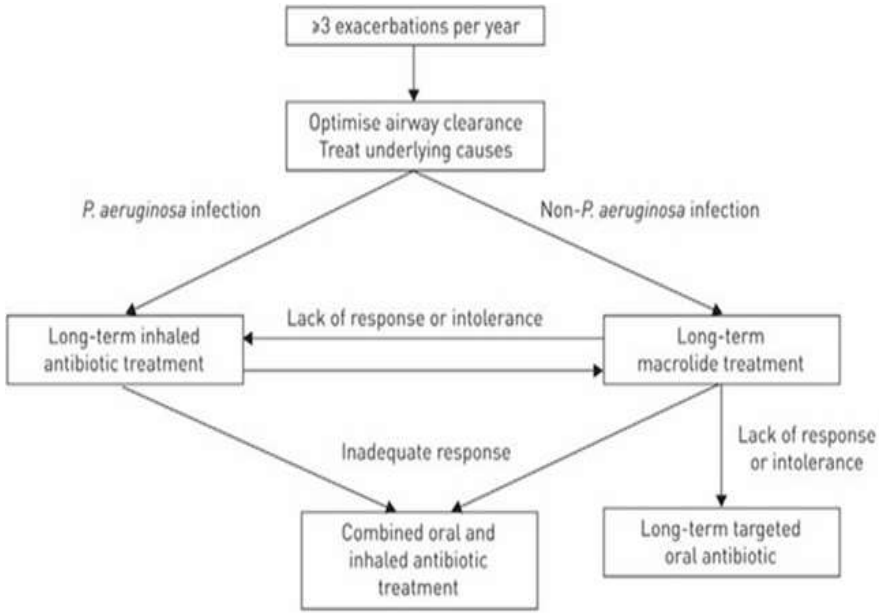


Fig. 4. European Respiratory Society Guidelines for long term antibiotic treatment in bronchiectasis [5].

(12).

If ≥3 AE/year and PSAE infection, initiate long-term inhaled antibiotic therapy. In case of inadequate response, combine with oral treatment. If there is no response/intolerance, consider long-term treatment with macrolides. If chronic non-PSAE infection and the same context of ≥3 AE/year, macrolides are recommended in the long term. If there is no response/intolerance, other options are targeted antibiotic therapy or combination with inhaled antibiotics.

- Chronic PSAE bronchial infection:

Inhaled antibiotic therapy allows the allocation of high therapeutic doses to airways with fewer systemic adverse effects(12). To do this, there are dry powder formulations (easier to use, implying less administration time and therefore associated with greater therapeutic adherence) and nebulizer formulations (with a lower risk of local adverse reactions and bronchospasm). Its use should be preceded by short-acting bronchodilators and mucolytics, as well as breathing exercises(15).

Therapeutic options include: tobramycin and colistimethate sodium (CMS), in solution for inhalation or dry powder, and aztreonam lysine (solution for inhalation)(14, 24). Ciprofloxacin (dry powder/solution for inhalation) and gentamicin (inhaled IV formulation) can also be used (24). Inhaled antibiotic regimens are done in 28-day on/off cycles (although the CMS allows continuous administration) and the total duration of treatment should be determined according to the therapeutic response (assessed between 3-6 months) and disease severity(15).

If inhaled antibiotic therapy does not work, add systemic antibiotic therapy(24) (Table 8).

Table 8 – Inhaled antibiotic therapy in chronic PSAE infection

Inhaled antibiotic therapy	**Dosage**	**Time of administration**	**Inhalation system TM**
Aztreonam lisina	75mg 3id, 28 days	2-3 minutes	e-Flow (Altera)
CMS dry powder	1662 U 2id, continuous	1-2 minutes	Turbospin
CMS Inhalational solution	1 UM 2id, continuous	4-6 minutes	I-neb AAS
Tobramicina dry powder	112mg 2id, 28 days	5 minutes	Podhaler (T-326)
Tobramicina Inhalational solution	300mg/ 5 ou 4mL	10-15 minutes	e-Flow; Pari LC plus

– Approach to acute exacerbations of BCs:

AE are responsible for disease progression and deterioration of lung function (2, 4). In its approach, it is important to consider the patient's microbiological history and the severity of AE. Generally, mild-moderate episodes involve oral antibiotic therapy for 10–21 days, while more severe AE should be addressed IV for 14–21 days (15, 24).

Among the most isolated microorganisms in the context of AE, the following stand out: PSAE, H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis and enterobacteria. Viruses may also be relevant in about 25% of AE (24). In a AE by PSAE, two anti-Pseudomonas antibiotics (such as a β-lactam and an Aminoglycoside) should be used(14).

5.5. Action on Bronchial Inflamation:

Although highlighting the need to address inflammation in BCs, the guidelines of the ERS and other scientific societies do not recommend the long-term use of agents such as statins or systemic or inhaled corticosteroids (ICS), namely because of the potential increased risk of NTM infection(11, 12).

Corticosteroid therapy and other anti-inflammatory drugs (NE inhibitors, antileukotrienes, phosphodiesterase 4 inhibitors) are not recommended in BCs, unless indicated by the coexistence of other comorbidities(1, 16, 24).

– Macrolides:

As mentioned in the approach to bronchial infection, macrolides are important therapeutic weapons in patients with BCs. Combining antibacterial, anti-inflammatory and immunomodulatory actions, they can improve the QOL of very symptomatic and/or exacerbating patients(14).

They modulate bronchial inflammation(15), influencing innate immunity (including neutrophil lung injury)(3, 19), decreasing the recruitment of eosinophils and neutrophils to airways and hindering the degranulation of the latter(12). They reduce the formation of neutrophilic NETs(19) and have beneficial effects on bacterial virulence, culminating in a significant reduction in AE over 6-12 months(3, 19), including infection with PSAE (an agent intrinsically resistant to the antibiotic effect of macrolides)(19).

– Brensocatib:

More recently, the role of Brensocatib in the inflammatory control of BCs has been tested. It is an oral, partial and reversible inhibitor of Dipeptidyl Peptidase 1 (DPP1 or Cathepsin C), an enzyme that activates serine-proteases of neutrophil granules and, therefore, potentially involved in neutrophil-mediated lung damage(3, 4, 25).

Inhibition of DPP1 prevents the activation of NE, Cathepsin G and Proteinase 3 in the bone marrow(9). A double-blind, randomized, placebo-controlled phase 2 clinical trial (CT) was shown to reduce AE without significant adverse effects(3, 4).

Currently in phase 3 of CT are anti-inflammatory anti-neutrophilic (NTC04594369) and anti- eosinophilic (NCT05006573) strategies, which may be opportunities to transform the approach to BCs(19).

5.6. Action on structural change:

The specificity and extent of irreversible bronchial dilatation underlying the concept of BCs condionate morbidity and contributes to the progression of the disease, representing one of the elements of the pathophysiological vortex of BCs that should be considered. Thus, structural lung disease in BCs may benefit from bronchodilator therapy and/or surgical approach(5, 12) – particularly in localized, unilateral and persistently symptomatic disease(9). Complications resulting from structural alterations (aspergillomas, lung abscesses, empyemas, severe hemoptysis that do not respond to bronchial embolization) may also require invasive approaches.

Palliative resections may be recommended in multi-lobule disease if a particularly affected segment is suspected of being a reservoir for recurrent infections(12).

In end-stage lung disease, with chronic, progressive and disabling respiratory failure, pulmonary hypertension, and estimated survival <2 years(14, 24), lung transplantation may be the only option.

5.7. Precision Medicine – Endotypes, Phenotypes and Traits Treatable:

The complex nature of BCs has been the subject of extensive research over the last few years, often seeking to classify the disease according to its etiology (endotype) and observable clinical characteristics (phenotype)(11), with a view to implementing precision medicine(1) – i.e., treatments targeted to the needs of each patient according to biomarkers, genetic, phenotypic and/or psychosocial characteristics that differentiate you from others.

Agusti A. et al (2016) proposed an approach to the disease of airways based on the identification of "Treatable Traits" in each patient, which contradicts the current rigid diagnostic view and guides towards a more precise treatment 32). Identification of endotypes, phenotypes, and treatable traits aids in the development of personalized medicine in a highly heterogeneous disease(12).

The concept of treatable traits encourages a holistic approach to patient care, around their major clinical problems (frequent AE, symptoms, other limitations) and treatable components of the disease, reinforcing the need to individualize care(1). To identify patients who respond best to certain treatments, it is important to define phenotypes (measurable characteristics consistent over time and related to relevant clinical outcomes) – e.g. existence of PSAE infection, frequency of AE, demographic (gender, age) or imaging characteristics,

presence/absence of sputum(11). Phenotyping consists of classifying a disease by the patient's observable characteristics. A phenotype reflects "what can be observed," including clinical, functional, imaging, and/or biological elements(32).

Endotyping refers to understanding a disease in terms of the underlying biological mechanisms(1). An endotype is a subtype of a condition that is defined by a distinct pathophysiological mechanism(9). It concerns the biological mechanisms, cellular and molecular pathways that participate in the pathogenesis of a disease, having a critical/important causal role in it(27, 32).

Identifying treatable traits (i.e., therapeutic targets as a function of endotypes and/or phenotypes) then allows for the guidance of precision medicine strategies(1).

Patients with BCs represent a heterogeneous group with multiple treatable traits that remain unrecognized (and therefore untreated). A treatable traits approach can contribute to more personalised and precise management(23). Agusti et al. divided the potential treatable traits of airways disease into 3 broad categories: Pulmonary, Extrapulmonary, and Behavioral/Lifestyle. A 4th category was then proposed to include "Etiological" treatable traits, emphasing the importance of identifying the traits that directly lead to the development of BCs(23). The combination of data resulted in the classification of BCs into 4 general categories:

Pulmonary, Extrapulmonary, Behavior/Lifestyle, and Etiology(11), which may be the target of personalized approaches (Table 9).

Table 9 – Treatable traits in bronchiectasis divided into pulmonar, aetiology related, extrapulmonary and behavioural/lifestyle (1)

Treatable trait	Identification	Treatment	Potential benefit
Pulmonary traits			
Infection	• Regular sputum culture • Sputum culture • Bacterial exacerbations	• Airway clearance • Antibiotic treatment for exacerbation • Long-term antibiotics	• Reduced exacerbations and reduced cough and mucus symptoms
Pseudomonas aeruginosa infection	• Regular sputum culture	• Airway clearance • Eradication at first isolation • Long-term antibiotics	• Reduced exacerbations and reduced cough and mucus symptoms • Improved quality of life
Mucus hypersecretion	• Volume and colour of sputum • Quality of life • CT scan showing mucus plugging	• Airway clearance • Devices • Mucoactive drugs • Anti-inflammatories (including macrolides)	• Reduce sputum volume • Improve airway clearance/ expectoration • Improve quality of life
Airflow obstruction	• Lung function testing	• Exercise/rehabilitation • Bronchodilators • Smoking cessation	• Improve symptoms and quality of life
Neutrophilic inflammation	• Sputum colour and volume • Frequency of exacerbations	• Macrolides • Antibiotic treatment for exacerbations/infection	• Prevent exacerbations and improve quality of life
Eosinophilic inflammation	• Blood eosinophil count >300 cells·μL^{-1} and frequent exacerbations	• Inhaled corticosteroids • Anti-IL5/anti-IL5 receptor monoclonal antibodies	• Prevent exacerbations and improve symptoms
Cough hypersensitivity	• Clinical features • Cough challenge	• Airway clearance • Physiotherapy	• Reduce exacerbations • Improve quality of life
Asthma	• Variable airflow obstruction • Bronchodilator reversibility	• Inhaled corticosteroids • Leukotriene receptor antagonists • Monoclonal antibodies	• Improve quality of life
NTM infection	• Positive cultures • Clinical and radiological features consistent with NTM pulmonary disease	• Antibiotic treatment • Airway clearance	• Improve quality of life • Achieve microbiological remission
Aspergillus sensitisation	• Elevated IgE and specific IgE to *Aspergillus* • Symptoms and exacerbations	• Oral corticosteroids • Antifungals • Inhaled corticosteroids	• Reduce exacerbations • Improve symptoms and quality of life
Bronchial hyperreactivity	• Bronchial challenge test	• Inhaled corticosteroid	• Reduce exacerbations
Respiratory failure	• Arterial oxygen and carbon dioxide	• Long-term oxygen or noninvasive ventilation	• Improve quality of life and/ or potentially survival
Aetiology related			
Immunodeficiency	• Serum immunoglobulins and functional antibodies	• Refer to immunology • Immunoglobulin replacement	• Reduce exacerbations and disease progression
Cystic fibrosis	• Clinical features • CFTR genetics and sweat chloride concentration	• Refer to CF clinic • CFTR modulators • DNase	• Improve lung function, quality of life and survival
Primary ciliary dyskinesia	• Clinical features • Nasal NO • Multidisciplinary diagnostics including high-speed video microscopy, EM, immunofluorescence and genetics	• Genetic counselling • Intensified airway clearance • Management of upper airway symptoms • Early introduction of prophylactic antibiotics	• Improve quality of life • Reduce disease progression • Prevent exacerbations
Inflammatory bowel disease	• Clinical features including classically sterile bronchorrhoea	• Refer to gastroenterology • Immunosuppression • Respiratory symptoms treated with inhaled corticosteroid	• Improve quality of life and symptoms
Connective tissue disease	• Clinical features and autoantibodies	• Refer to rheumatologist • Immunosuppressive drugs with early introduction of prophylactic antibiotic	• Improve quality of life • Prevent exacerbations

Treatable trait	Identification	Treatment	Potential benefit
Extrapulmonary traits			
Depression/anxiety	• Symptoms/patient history • Questionnaires	• Cognitive behaviour therapy • Counselling • Pharmacotherapy • Support groups	• Improve quality of life
Obesity/low BMI	• BMI	• Nutritional evaluation • Good diet • Regular physical activity	• Improve quality of life
GORD	• Clinical features • Endoscopy • pH monitoring	• Lifestyle advice • Proton pump inhibitor or equivalent • Surgery	• Improve quality of life • Reduce exacerbations
Cardiovascular disease	• Clinical features • Echocardiography and ECG • BNP • Stress testing	• Pharmacotherapy for heart failure of ischaemic heart disease • Refer to cardiology	• Improve exercise capacity and quality of life
Rhinosinusitis	• Clinical features • Imaging	• Nasal steroids • Leukotriene receptor antagonists • Antihistamines • Macrolides • Surgery	• Improve quality of life • Reduce exacerbations
Anaemia	• Full blood count • Reticulocyte count • Haematinics	• Treat underlying cause	• Improve exercise capacity
Behaviour/lifestyle traits			
Exercise deconditioning	• Cardiopulmonary exercise testing • Other exercise tests	• Regular exercise • Pulmonary rehabilitation	• Improve exercise capacity and quality of life
Treatment adherence	• History • Electronic prescribing data	• Education • Self-management • Shared decision making	• Improve quality of life • Prevent exacerbations
Air pollution exposure	• Exposure to pollutants	• Reduce exposure	• Reduce exacerbations
Smoking (including vaping and electronic cigarettes)	• Patient reported	• Smoking cessation including replacements and pharmacotherapy	• Improve quality of life and lung function • Reduce exacerbations

Table adapted from Bonaventura *et al.* [88]. BMI: body mass index; BNP: brain natriuretic peptide; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CT: computed tomography; DNase: deoxyribonuclease; EM: electron microscopy; GORD: gastro-oesophageal reflux disease; IL: interleukin; NO: nitric oxide; NTM: nontuberculous mycobacteria.

(Table from Chalmers JD, Elborn S, Greene CM. Basic, translational and clinical aspects of bronchiectasis in adults. EurRespirRev2023;32:230015[DOI:10.1183/16000617.0015-2023])

6. Monitoring and Follow-Up

The frequency and intensity of follow-up depend on a number of factors, including the initial severity of the disease(24). Factors associated with worse outcomes and increased morbidity and mortality include high scores for dyspnea, deteriorated pulmonary function, radiological extent of the disease, chronic PSAE infection, and frequent hospitalizations and exacerbations(3).

Overall, at least one evaluation in consultation every 6-12 months is recommended(24), and it is important to reassess signs and symptoms, ensure maintenance of therapeutic adherence, inquire about possible complications, as well as AE (number and severity)(15) (Table 10).

Table 10 – Proposal for monitoring and follow-up of the patient with BCs (15)

	Mild illness	**Moderate-severe disease**
Etiological investigation	At diagnosis	At diagnosis; repeat if justifiable
Assessment of comorbidities	Annual	
Severity Scores	Annual	
Body Mass Index	Annual	
Symptoms, Episodes of AS, Sputum culture	Each Consultation	
Spirometry	Annual	
PM6M	Annual	
Analyses (with acute phase, total IgE and Aspergillus fumigatus parameters)	Annual	
Chest X-ray	If complications, pneumonia/pneumothorax is suspected	
HRCT scan	Every 5 years or earlier if clinical and/or functional worsening	
Review of medication, inhalation technique and secretion drainage	Each Consultation	

7. Conclusion

With a view to the optimal control of the disease and its progression, the etiological study of BCs and the approach of the various pathophysiological elements involved, along with general measures of harmful avoidance and health promotion, remain crucial in any patient.

However, as a result of the growing recognition of the complexity surrounding BCs, there is an increasing change in the paradigm of its approach. The definition of endotypes and phenotypes, with the associated identification of treatable traits, enables the choice of treatments directed to the particularities of each patient and with fewer unnecessary adverse effects.

BCs are – today more than ever – a fertile and promising field for research and therapeutic development, in a logic that “one size does not fit all”.

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