

Non Cystic Fibrosis Bronchiectasis-new clinical approach, management of treatment and pulmonary rehabilitation

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Abstract

Non-Cystic Fibrosis Bronchiectasis (NCFB) are characterised by abnormal, permanently damaged and dilated bronchi due to the inappropriate clearance of various microorganisms and recurrent chronic infections. The diagnosis is suggested by the clinical presentation and is confirmed by multiple investigations. There are some comorbidities associated with bronchiectasis, such as chronic obstructive pulmonary disease (COPD), cardiovascular disorders, gastro-esophageal reflux disease (GERD), psychological illnesses, pulmonary hypertension, obstructive apnea syndrome (OSA). The condition has a substantial socioeconomic impact because it requests a multidisciplinary management and periods of exacerbations are common. The aims of the management of bronchiectasis are to reduce symptoms (such as sputum volume and purulence, cough and dyspnea), reduce the frequency and severity of exacerbations, preserve lung function and improve health-related quality of life. The multidisciplinary approach of bronchiectasis patients require along with the medical treatment, a specific plan of nonpharmacological strategies, including balneological intervention. There are a lot of techniques improving the airway clearance, such as: active cycle of breathing techniques (which include breathing control, thoracic expansion exercises, forced expiratory technique), oscillating positive expiratory pressure, autogenic drainage, gravity-assisted-positioning, modified postural drainage. Together with specific medication, these techniques can diminish symptoms and improve the quality of life.

Key words: *NCFB, airway clearance, physiotherapy,*

Introduction

Non-Cystic Fibrosis Bronchiectasis (NCFB) is a chronic debilitating condition, first described by René Laennec in 1819. This condition is characterised by abnormal, permanently damaged and dilated bronchi, due to chronic bronchial inflammation because of inappropriate clearance of various microorganisms and recurrent or chronic infection (1). However, in a substantial number of patients no cause is found (2). Symptoms vary from intermittent episodes of respiratory infections with excessive mucus production to chronic symptoms with persistent daily expectoration of purulent sputum. It is a debilitating illness responsible for significant morbidity, with patients typically suffering from intermittent episodes of respiratory infections with excessive mucus production to chronic symptoms such as a persistent cough, daily sputum expectoration, recurrent chest infections and a poor health-related quality of life (3). The condition has a substantial socioeconomic impact because it request multidisciplinary management and periods of exacerbations are common (4).

Prevalence

Even if once NCFB was a very rare diagnosis, in the last two decades its prevalence has varied among populations and several studies have reported a prevalence ranging from 486 to 1106 per 100000 persons (5-7). The incidence of non-cystic fibrosis bronchiectasis is 2–5 patients per 1,000 population (8). It was observed that this pathology is more frequent in women and older individuals and many patients tend to have a more severe and symptomatic disease. Bellelli G et al. reported in one study of over 1,200 patients with bronchiectasis, 50% were over 65 years old and 19.1% were over 75 years (9). Increasing age is recognized as an independent risk factor for bronchiectasis severity (10). There is still a high incidence in developed countries and globally with the increased life expectancy of the general population, there is a greater risk of more people developing chronic illness, including bronchiectasis (11).

Patophysiology

The aetiology of NCFB is variable, but the common pathophysiological pathway represents a vicious cycle containing three important elements: inflammation, infection and damage on the bronchial wall. Potential causes of this breach include severe lower respiratory tract infections, gastric aspiration and/or inhalation of toxic gases, immunoglobulin deficiency, ciliary dysfunction, connective tissue disease, rheumatoid arthritis-related, airways disease (asthma/COPD), non-tuberculosis mycobacterium, foreign body inhalation, inflammatory bowel disease-related. These modifications, through local or systemic inflammation, cause disturbances in the architecture of bronchial airways (12,13).

The usual mucociliary clearance defence mechanism is impaired, so the airways become chronically infected with a variety of bacteria which promotes further neutrophilic inflammation. Once the bacterial density in the airways is increasing, there is an exaggerated inflammatory response consisting of greater numbers of neutrophils and higher concentrations of neutrophil degradation products beside other inflammatory markers (14).

So, the patient with NCFB is enrolled in a vicious cycle of infection and inflammation developing persistent symptoms, frequent exacerbations and further airway damage (15). These modifications such as host inflammatory response and microbial cytotoxins, cause additional structural damage of the lung and further impair mucus clearance, so it is easier for the microorganisms to form biofilms (16). The role of the biofilms is to protect the bacteria from the clearance of the host immune system which reduce the effects of antibiotics further potentiating airway inflammation (17).

Clinical Presentation

Non-cystic fibrosis bronchiectasis can be presented as asymptomatic, or in some individuals can cause massive haemoptysis and respiratory failure, so the most common clinical presentation is between these extremes. In one study of 103 adults with NCFB, 98% reported a chronic cough, and 76% of patients had daily sputum production. From common presenting symptoms, dyspnoea occurred in 62% of cases and chronic fatigue was reported by 74% of subjects (18,19). Moreover, intermittent haemoptysis occurred in 26-51% of cases, which at times became life-threatening (19). On the other hand, many

patients with bronchiectasis require frequent hospital admissions for recurrent pneumonia(18) and depression or anxiety which may significantly affect their quality of life (20).

Investigations

Physical examination and history contribute to the diagnosis of bronchiectasis. The most common modifications include crackles (73% of subjects), rhonchi (44%) and wheezing (21%-34%) (18).

The first tool to evaluate a patient with bronchiectasis is a standard chest radiography which can detect multiple areas of bronchial wall dilatation in subject with moderate to severe bronchiectasis. However, studies have evidenced that chest radiography has moderate sensitivity(88%) and poor specificity (74%) for the detection of bronchiectasis (21).

The current gold standard for the diagnosis and confirmation of bronchiectasis is high-resolution computed tomography(CT). The characteristic feature of NCFB by CT is bronchial wall dilatation with the luminal diameter greater than 1-1.5 the size of the accompanying pulmonary artery branch. Other findings include absence of normal tapering of the bronchi, bronchial wall thickening, mucoid plugging of the airways and proximity of visible airways close to the pleura (22).

On the other hand, pulmonary function testing is often used to evaluate the subject with chronic pulmonary diseases. Patients with bronchiectasis usually present mild to moderate airway obstruction, with a forced expiratory volume in the 1st second (FEV1)/forced vital capacity (FVC) ratio less than 70 and a FEV1>50% of predicted. In 22% of cases with NCFB, there is a significant bronchodilator response(18). Some conditions are associated with more severe obstruction, such as: a history of Pseudomonas infection or colonisation, multilobar involvement of disease, greater purulent sputum volume and those patients with at least four exacerbations over a 2-year period (23).

In addition, sputum culture must be obtained from all patients with bronchiectasis. The most common organisms initially isolated are Gram negative bacteria including Haemophilus influenzae (47%), Pseudomonas aeruginosa (12%) and Moraxella catarrhalis (8%). After a period of time, Pseudomonas aeruginosa becomes more frequent. All in all, Gram-positive bacteria such as Streptococcus pneumoniae and Staphylococcus aureus are rare (24).

In the last decades, Non-tuberculosis mycobacterium (especially *Mycobacterium avium*) incidence has increased accounting for 2-30% of pathogens isolated (25).

Once bronchiectasis is confirmed based on clinical presentation and radiographic imaging, determining the underlying cause is important to effective therapeutic management. First of all, both primary and secondary immunoglobulin deficiency (in particular IgG deficiency) should be tested because it can be associated with bronchiectasis and the frequency of infections can often be reduced by immunoglobulin replacement therapy. All patients should undergo testing for allergic bronchopulmonary aspergillosis (ABPA), depending on radiological features (temporary infiltrates are seen initially and it can eventually lead to proximal bronchiectasis) and tests to confirm aspergillus hypersensitivity (raised peripheral blood eosinophils, total IgE, Aspergillus specific IgE or positive skin test with or without aspergillus precipitins) (26).

Comorbidities

The possibility of coexisting inflammatory bowel disease, connective tissue disease or vasculitis. Comorbidities are more likely in the elderly and clinical suspicion will warrant relevant screening such as ANCA, anti-CCP, fecal calprotectin etc. Bronchiectasis associated with a connective disease such as rheumatoid arthritis is often more aggressive and carries a worse prognosis (26).

In addition, several other pathologies may occur at any stage of bronchiectasis and are likely major contributors to increased hospitalisations, healthcare utilisation and socioeconomic costs (27). These include COPD, cardiovascular disorders, gastroesophageal reflux disease (GERD), psychological illnesses, pulmonary hypertension, obstructive apnea syndrome (OSA), cognitive impairment, lung, oesophageal and hematological malignancies (20,28-29). One of the important comorbidities is OSA, but the relationship between sleep disorders and bronchiectasis has not been well described. There is an assumption that, due to the irreversible dilatation of the bronchi, the presence of secretions, and airflow obstruction, patients with non-cystic fibrosis bronchiectasis may be predisposed to hypoxemia during sleep, or to symptoms that may lead to arousal (30).

The importance of screening programs for comorbidities, such as OSA and diabetes mellitus type 2 is evident in bronchiectasis patients, moreover because some studies showed that only being overweight itself produces a greater risk of developing a metabolic syndrome and sleep disorders (31).

Management

The aims of the management of bronchiectasis are to reduce symptoms (such as sputum volume and purulence, cough and dyspnea), reduce the frequency and severity of exacerbations, preserve lung function and improve health-related quality of life.

In the multidisciplinary management, every respiratory physician must take into account the gravity score. There are several scales of severity. One of them is the one proposed by Chalmers et al. who introduced the bronchiectasis severity index (BSI), including High resolution Computed Tomography (HRCT) score, FEV1, Medical Research Council dyspnoea score, bacterial colonisation (*Pseudomonas aeruginosa* or other pathogenic bacteria), prior hospital admission and exacerbations. They conclude that the BSI was a sensitive tool in predicting future risks of hospitalisation (10). On the other hand, Martinex-Garcia et al. (32), established the FACED score, a simpler one, which includes FEV1, age, *Pseudomonas aeruginosa* colonisation, radiological extension and dyspnoea. Similarly, the FACED score effectively predicted mortality.

The first step of the management is the patients' education; they should understand the diagnosis in order to limit other injury to the airways, by smoking cessation, limiting infective insults, prevention of viral infections by receiving the annual seasonal influenza vaccination (33-34). Also, in obese patients, diet is one of the most important interventions along with a training program in order to reduce body mass index (BMI), improve sleep quality and increase respiratory muscle endurance in patients with bronchiectasis and other comorbidities, such as OSA, but in selected cases with associated craniofacial deformities, early orthodontic treatment could be necessary (35,36,37). Also, weight loss improves the cardiovascular status, moreover because obese patients develop a metabolic syndrome which can be fatal for bronchiectasis patients because it can reduce their effort capacity and their quality of life (38).

The multidisciplinary approach of bronchiectasis patients requires along with the medical treatment, a specific plan of nonpharmacological strategies, including balneological intervention: an active cycle of breathing techniques (which include breathing control, thoracic expansion exercises, forced expiratory technique), oscillating positive expiratory pressure, autogenic drainage, gravity-assisted-positioning, modified postural drainage.

Airway clearance

Airway clearance techniques (ACT) are nonpharmacological strategies used worldwide in order to improve symptoms, reduce exacerbation frequency and increase quality of life (39). There are some short terms goals of ACT such as more effective sputum clearance which has been proven to improve ventilation, reduce cough impact and breathlessness. On the other hand, its long-term effects are reducing airway damage by stopping the vicious cycle of colonization and subsequent inflammation, reducing the number of exacerbations and hospitalizations and improving the quality of life (40).

ACT are a key component in the management of patients with bronchiectasis, moreover for patients with a chronic productive cough or difficulty expectorating sputum which may benefit from regular twice daily ACT as recommended in the current guidelines (41). Active Cycle of Breathing Technique (ACBT) is a repetitive cycle consisting of 3 distinct components: breathing control (BC), thoracic expansion exercises (TEE), and the forced expiration technique (FET). The cycle and length of each component are flexible and can be adapted to individual needs. BC is relaxed tidal breathing using the lower chest and performed at the patient's own rate. Its role is to minimize any flow obstruction. TEE are dynamic procedures and are performed by taking deep slow inspirations through the nose (if possible), followed by an inspiratory pause with an open glottis, and subsequently relaxed expiration, in order to mobilize the secretions. The FET is a principle component of the ACBT and is defined as a combination of 1 or 2 forced expirations (huffs) interspersed with periods of BC. The lung volume can be varied depending on which segment to target. For example, FET from high lung volumes helps to clear secretions, whereas FET from low lung volumes helps to mobilize secretions. The FET aims to move the mobilized secretions to the proximal airways to be

cleared, which then may subsequently require a cough (42). However, in practice ACT remains underutilized, as showed by The European Bronchiectasis Data Registry (EMBAC) that reported that only 45% of patients perform ACT regularly (43,44). ACT has two main principles: to ventilate the regions distally, behind the obstruction and to modulate the expiratory airflow to propel secretions proximally up the airways. So, to enhance the mucus clearance, the peak expiratory flow rate should be at least 30-60 l/min and greater than the inspiratory flow (44). Other techniques used in patients with bronchiectasis are: oscillating positive expiratory pressure (PEP), autogenic drainage (AD) and ELTGOL (active technique where the patients carries out slow expiration with the glottis open in a lateral decubitus position).

PEP uses a set resistance that is applied throughout expiration to enhance the mobilization of secretions, by using either a mask or a mouthpiece attachment and induces a temporary increase in functional residual capacity. Moreover, it facilitates collateral ventilation, and encourages the recruitment of closed airways. Furthermore, it may splint airways open, aiding expiratory airflow, because airways are often prone to collapse during active expiration as a result of increased intrathoracic pressure (45,46). Autogenic drainage (AD) is a 3-phase breathing programme using high expiratory flow rates at varying lung volumes to facilitate mucus clearance. It requires a progressive volume increase in order to maximize expiratory flow velocity to produce shearing forces and move secretions. Inspiration should be low flow with an inspiratory pause and open glottis. Expiration should be a higher flow, although aiming to minimize airway collapse (47,48).

Considering the studies, Patterson et al. demonstrated that ACBT versus oscillating PEP had no improvement in lung function or sputum weight over a 10-14 day treatment period in 20 stable patients (49). This idea was sustained in the study of Thompson et al. who also took into consideration the quality of life, which was not improved after a 4-week treatment period (50). In a study performed by Herrero Cortina et al., both AD and ELTGOL resulted in significantly greater sputum compared to the control group (51). Another study, involving ELTGOL, made by Munoz et al. which compared the ELTGOL technique to placebo exercises twice daily in 44 patients over a 1-year period, reported fewer

exacerbations, reduced cough impact and improvement in the quality of life in the therapy group (52).

Another technique is gravity-assisted positioning (GAP) which is passive and relies solely on the effects of gravity and changes in regional ventilation with positioning, so it cannot be used alone as an ACT. Patient position themselves to drain specific lobes within the lungs, using gravity to enhance movement of secretions. For example, the lower and middle zones of the lung drain includes a head-down tip position. Studies showed that the performance of ACTs in GAP positions may help enhance sputum clearance (53). Modified postural drainage (MPD) uses similar specific lobar drainage positions as in GAP, but eliminates any head-down tip, thus using gravity neutral positions. MPD is recommended in patients that have contraindications for GAP, for examples in subjects which are associated with GORD. Cecins et al assessed the effectiveness of modified positions without a head-down tip and showed no significant difference in MPD versus GAP, because the results of sputum weight did not vary more than 15% (54).

These studies with interventions longer than a single treatment demonstrate some proof of the concept on the effectiveness of ACT in bronchiectasis and support the general consensus that currently no one ACT is superior in terms of clinical outcomes (55). There is wide variety of techniques that are age, preference and co-morbidity dependent, so the selection of ACT should be targeted according to the patient's individual characteristics (56). Taking into consideration the comorbidities, such as OSA, the airway clearance is very important because the presence of various microbiological and inorganic structures on the inner surface of CPAP masks and tubes emphasizes the risk of microbial and inorganic elements inhalation into the upper and lower airways. Therefore, the microclimate and the hygiene of CPAP device, including masks and tubing is very important in order to reduce exacerbations (57-58). Also, patients with bronchiectasis should reduce their exacerbation risk by limiting air pollution both indoor and outdoor and the exposure to allergens (59).

Airway humidification

The aim of airway humidification (with molecular water added to gas) is to reduce mucus viscosity and enhance flow through the airways. There are a few

studies on this subject, which demonstrated that airway humidification increases airway clearance and sputum yield, so can be used in addition to ACT. However, the evidence is insufficient to recommend it for routine use in subjects with bronchiectasis (60).

Mucoactive therapy

Studies showed that mucoactive therapy should be considered if ACT are not effective (41). Mucoactive medications potentially increase the ability to expectorate sputum and/or decrease mucous hypersecretion and should be coordinated with ACT to ensure the overall effect is optimized. As Balsamo et al. showed, they can broadly be characterized into several major groups based on their potential mechanism of action (61):

1. Expectorants are drugs that induce discharge or expulsion of mucous from the respiratory tract. Typically, this requires a coughing action to loosen and bring up the mucous from the lungs or upper respiratory tract. Examples include hypertonic saline (HTS) and a solution of manitol.
2. Mucoregulators: drugs that regulate mucous secretion or interfere with the DNA/F-actin network. Examples include carbocysteine and anticholinergic agents.
3. Mucolytics: drugs that decrease mucous viscosity. Examples include N-acetylcysteine, erdosteine and DNase.
4. Mucokinetics: drugs that increase mucociliary clearance by acting on the cilia. Also referred to as cough clearance promoters. Examples include bronchodilators and surfactants (61).

The European Respiratory Society (ERS) guidelines (62) summarize the findings of three systematic reviews that have comprehensively examined the current evidence for mucoactives (63-65). It was proven that none of the mucoactive agents significantly reduced the number of exacerbations, but one trial with 88 participants showed that high doses of bromhexine with antibiotics significantly eased difficulty in expectoration and sputum production days compared to a placebo (66). HTS action is achieved by altering the concentration of water in the mucus but, clinical trials are limited. However, it was evidenced that it is responsible for yielding greater sputum weights with greater ease and less viscosity (67). The manitol role is to enhance mucociliary clearance with improved mucus

clearance for up to 24 hours after inhalation and it was demonstrated that it has an important positive effect on small airways function, cough transportability and health-related quality of life (68). The prescription of mucoactive therapies should be done in addition to ACT and therefore it is important that the mechanism of action of mucoactive drugs and their timing with ACT are taken into consideration. In case of HTS which has a short-term/immediate effect, the ACT should be done immediately after HTS inhalation (69). There are two active clinical trials exploring the efficacy of commonly used mucoactives (HTS and carbocisteine) in bronchiectasis. The results are likely to have an important impact on future practice (70-71), moreover because there is stronger evidence for carbocisteine and HTS in other conditions and these are the most commonly used mucoactives in bronchiectasis (72). Regarding inhaled mucolytics, their role is to cleave the excessive quantities of DNA accumulated due to neutrophil activity, reduce sputum viscosity, improve expectoration, airway clearance and lung function. However, it is not recommended in routine use because of its side effects with the decline of FEV1, higher rate of exacerbations, increased use of antibiotics and a greater rate of hospitalisations (73). On the other hand, inhaled corticosteroids are recommended to be used in the treatment of bronchiectasis together with rehabilitation programmes where there is co-existing obstructive airways disease such as asthma, COPD or ABPA (74). The British Thoracic Society (BTS) bronchiectasis guidelines recommend a trial of bronchodilator therapy if shortness of breath affects the patient's activities of daily living. In these situations it is worthwhile to perform a trial of short-acting beta-agonist (SABA) or short-acting muscarinic-antagonist (SAMA) initially and if there is clinical benefit then proceed to a long-acting bronchodilator (75).

Antimicrobial therapy

The number of clinical trials investigating antibiotic therapy in NCFB is small, but has been administered systemically or via inhalation (76). However, chronic treatment is not recommended and the most effective antibiotics are macrolides. They act with an anti-inflammatory effect, reducing the total bronchoalveolar lavage cell count, sputum volume and interleukine 8 and neutrophil activity. Also, Anwar et al. showed an improvement in exacerbation

frequency, spirometry and sputum microbiology when treated with azithromycin 250 mg three times a week (77). However, inhaled antibiotics have more limited side effects, but may be less tolerated because of the bronchospasm. For example, inhaled tobramycin decreased the number of admissions and days in the hospital and it has been showed that by prolonging their use may appear a positive effect. Also, there are continuous improvements in drug design, with aerolised formulations that are well tolerated by the epithelial surface, able to penetrate infected sputum and capable of avoiding immune system clearance in order to achieve a better therapeutic response (78).

Pulmonary rehabilitation

Pulmonary rehabilitation, with patient-centred exercise training and collaborative self-management education delivered by an interdisciplinary team and centred on the specific needs of the patient (30), has evolved beyond the confines of chronic obstructive pulmonary disease (COPD) management. Pulmonary rehabilitation must take into account the patients' comorbidities. In general, PR incorporates several exercise modalities (treadmill walking, cycle ergometry, weight lifting and arm ergometry) and patient education and works through secondary impairments such as peripheral muscle dysfunction, psychosocial dysfunction and maladaptive behaviours (79). It is necessary that patients be educated once the pulmonary rehabilitation programme is initiated to minimize their exposures to respiratory irritants. In this direction, smoking cessation is crucial in addition to the avoidance of air pollution, both outdoor and indoor (radon exposure) (80,81,82). Exercise training (ET) programmes are comprised of the exercise modalities without an educational component. PR and ET programmes are generally aimed at improving both upper limb and lower limb endurance and are tailored to the needs of the individual patient. The location of the programmes vary: some are incorporated into hospital-based physical medicine and rehabilitation medicine facilities; others are free standing and may even be in a community centre or in an outpatient physiotherapy department. Based on the location of the exercises, the trained staff may include: exercise physiologists, respiratory care practitioners, physiotherapists and nurses. Also, the patients participating in PR or ET are generally monitored

with oximetry and occasionally cardiac monitoring. The duration of the programs vary: in the United States, these programmes are generally comprised of an initial intensive phase which includes 36 1-hour sessions over 12 weeks followed by a self-guided maintenance phase, but in other parts of the world, the patients may receive shorter or longer periods of supervision (79).

A recent systematic review confirmed the short-term benefits that patients achieve from participating in supervised PR and ET, but noted that sustaining benefit is challenging (83). However, the study of Ong et al., suggested that despite the absence of a structured maintenance program, the 6-minute walking distance remained significantly higher than baseline at 12 months and the chronic respiratory disease questionnaire (CRQ) scores similarly remained stable for 12 months (84). In addition, Newall et al. which conducted the first study to assess the effects of exercise training in patients with bronchiectasis showed that an 8-week PR program was effective in improving the exercise capacity and health status, regardless of the addition of inspiratory muscle training (85). Moreover, Mandall et al., in one study comparing PR and chest physiotherapy versus chest physiotherapy alone in 30 patients with bronchiectasis, observed short-term improvement in PR outcomes, with a reduction in the frequency of exacerbation after 12 months, as well as an improvement in the walking distance (86).

The physiological rationale for PR and ET in bronchiectasis is that muscle weakness and physical inactivity may play a role in disease progression as well as impact the quality of life, frequency of infectious exacerbations and the ability to mobilize secretions (87). One observational study of 41 patients with bronchiectasis showed that PR significantly improved forced vital capacity and residual volume measurements (88). Lee et al., concluded in one study that compared ET with airway clearance training to standard care that there was an improvement in exercise capacity, dyspnoea and fatigue as well as fewer exacerbations over 12 months (89). Patients that cannot perform ET, can benefit from neuromuscular electrostimulation (NMES) which has been extensively used as a technique to improve muscle function and structure in different areas of rehabilitation and sport training programs (90).

Conclusion

Non cystic fibrosis bronchiectasis is a chronic, inflammatory lung disease that is characterized by a chronic cough, daily sputum production, and frequent exacerbations. There is a spectrum of disease, ranging from minor symptoms to a severe and progressive condition that can result in overwhelming infection or respiratory failure. It has become increasingly recognised that treatments for bronchiectasis cannot be extrapolated from other chronic respiratory diseases and more studies are required both to better understand the disease pathogenesis and to establish the optimum multidisciplinary approach to the management of this debilitating disease. Pulmonary rehabilitation is a comprehensive and effective treatment approach that improves overall clinical status and increases the level of physical activity in patients with bronchiectasis. It is essential that patients with bronchiectasis are included in comprehensive PR programs that are planned based on the patients' current clinical status and individual needs, in order to increase their quality of life.

Conflict of interest

There is no conflict of interest for any of the authors regarding this paper.

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