Review

Update on the management of patients with non cystic fibrosis bronchiectasis

Katerina Dimakou[1],
Michail Toumbis[2],
Christina Triantafillidou[2]

[1]5th Pulmonary Clinic, Sotiria Chest Diseases Hospital,
[2]6th Pulmonary Clinic, Sotiria Chest Diseases Hospital,
Athens, Greece

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ABSTRACT. Bronchiectasis not due to cystic fibrosis (non CF bronchiectasis) is an underdiagnosed disease, while recently an increase in the prevalence and hospitalizations for bronchiectasis has been reported, causing a substantial burden on healthcare systems. The goal of the appropriate management of patients with non CF bronchiectasis is to cease the "vicious circle" of bronchiectasis. After an initial thorough aetiological investigation, general measures should be offered that include smoking cessation, vaccination against influenza and pneumonococcal infection and oxygen supplementation if respiratory failure occurs. Antibiotics are the cornerstone of treatment. The appropriate antibiotic regimen guided by sputum culture is of great importance in exacerbations of bronchiectasis, while certain algoriths exist for the eradication of Pseudomonas aeruginosa. Long term macrolides and inhaled antibiotics are recommended for patients chronically colonized with P.aeruginosa and in patients who present ≥3 exacerbations per year or even in case of fewer exacerbations but with significant morbidity, as they have shown positive effects in sputum volume and purulence, they reduce the risk of exacerbations and improve symptoms and quality of life. A subset of patients with a significant bronchodilator response and obstructive lung function pattern may benefit from inhaled β2-agonists and/or inhaled corticosteroids. Airway clearance techniques and pulmonary rehabilitation have been found to improve sputum expectoration, reduce hyperinflation and quality of life. Bronchial arterial embolization is the treatment of choice in cases of severe or reccurent haemoptysis, while surgery for bronchiectasis is extremely rare nowadays. New therapies are currently under consideration, while updated recommendations and guidelines are under preparation. *Pneumon 2015, 28(3):251-257.*

Correspondence:
Dimakou Aikaterini
152 Mesogion Ave., 11527 Athens, Greece
E-mail: kdimakou@yahoo.com

INTRODUCTION

Bronchiectasis is a chronic pathologic description of lung damage, characterized pathologically and radiologically by permanent dilatation

of the bronchi and clinically by a syndrome of cough, sputum production and recurrent respiratory infections[1]]. Bronchiectasis is not itself a disease but rather the result of various processes. Bronchiectasis not due to cystic fibrosis (non CF bronchiectasis) is an underdiagnosed disease and sometimes it is regarded as a condition in which extensive investigation is unlikely to lead to treatable causes[2,3]. While the diagnosis of bronchiectasis has become easier with the advent of HRCT which is considered the gold standard for diagnosing bronchiectasis[4,5], the prevalence of bronchiectasis is not precisely known and it is rather underestimated. An increase in the prevalence and hospitalizations for bronchiectasis has been reported over recent years in Europe and the USA as well, causing a substantial burden on healthcare systems[6].

The goal of the appropriate management of patients with non CF bronchiectasis is to cease the "vicious circle" of bronchiectasis which consists of chronic colonization by potentially pathogenic microorganisms which represent a risk for respiratory infections, and may cause the release of several inflammatory mediators that lead to impaired mucociliary clearance and progressive tissue damage that facilitates further colonization.

The aim of this short review is to provide an update on therapy of non CF bronchiectasis according to recent trials and guidelines focusing on treatment strategies to eradicate and prevent airway bacterial colonisation, to reduce airway inflammation, to improve physical functioning, quality of life and airway mucus clearance.

AETIOLOGICAL INVESTIGATION

The first step in the management of patients with non CF bronchiectasis is to assess and treat the underlying causative factor. However, quite often, no underlying cause is identified, reported in a rate of 35 to 53% for some studies[1,2,7]. In a recent Greek report, an obvious aetiology was not identified in 34% of 277 patients with non CF bronchiectasis (Figure 1)[8]. Post-infectious bronchiectasis is the most common cause of non CF bronchiectasis although often considered as an overestimate due to recall bias[6]. Other common causative factors are immune deficiency, tuberculosis (TB) and non TB mycobacterium infection, primary ciliary dyskinesia (PCD), allergic bronchopulmonary aspergillosis (ABPA), primary bronchiolar disorders, inflammatory bowel diseases, COPD, bronchial asthma, congenital disorders, rheumatoid arthritis, aspiration, chronic obstruction of bronchus and

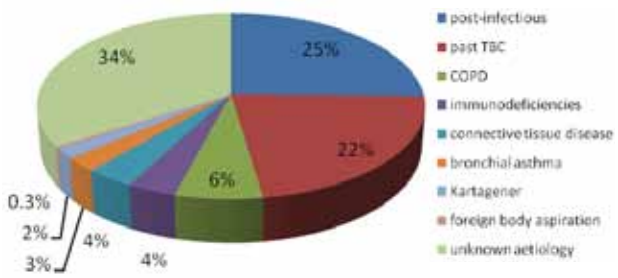

FIGURE 1. A pie diagram showing the aetiological factors in a greek cohort of 277 patients with non CF bronchiectasis (from reference 8).

other rare syndromes[3]. According to current guidelines of some european countries, investigation directed at the underlying cause should include for most patients measurement of serum immunoglobulins IgA, IgM, IgG and IgE, serum electrophoresis and testing to diagnose or exclude ABPA (specific IgE to Aspergillus or skin prick test, IgG to Aspergillus and blood eosinophil count)[3,9,10]. Further investigation should be directed according to the patients' clinical, laboratory and radiological characteristics and may include sputum culture for tuberculosis (TB) and non-TB mycobacterium, autoantibodies testing, α1-antitrypsin measurement, or bronchoscopy. Additional investigation for asthma and COPD as an underlying condition is necessary. Ciliary function tests are also suggested in adults who present with a history of chronic upper respiratory tract problems or otitis media since childhood, especially in the presence of predominantly middle lobe bronchiectasis and infertility or dextrocardia, while testing for CF by sweat test and common CFTR genetic mutation analysis is recommended for patients aged <40 years or with persistent colonization with Pseudomonas aeruginosa and Staphylococcus aureus in the sputum, upper lobe predominant disease, malabsorption, infertility or a history of childhood steatorrhoea irrespective of age[3]. Therefore, specific treatments such as immunoglobulin replacement, steroids and anti-fungals for ABPA, adequate treatment for TB and non-TB mycobacterium or referral to a specialist centre for CF are very important with respect to the underlying cause for every patient individually[3,9].

MANAGEMENT

In order to evaluate and manage patients with bronchiectasis properly, a HRCT of the chest, lung function testing and an assessment of lower respiratory tract

microbiology by obtaining sputum culture are necessary. In all bronchiectatic patients general measures should be offered and should include smoking cessation guidance, vaccination against influenza and pneumonococcal infection, oxygen supplementation if respiratory insufficiency occurs and management of co-morbidities[3,9].

Recently, the bronchiectasis severity index (BSI), a very useful clinical prediction tool has been introduced and can be easily used by physicians in order to identify patients at the highest risk of complications, including exacerbations, and predict mortality as well[11]. This scoring system can also serve as a valuable tool for the management of bronchiectatic patients in order to stratify therapy according to the severity of their disease individually.

Antibiotics

Exacerbations of bronchiectasis is a major issue as it is the main cause of morbidity, affecting quality of life and severity of the disease, and inevitably lead to a significant financial burden on health-care resources[11]. Antibiotics are recommended for patients who present with an acute deterioration with worsening symptoms, increased sputum volume or increased sputum purulence[3,9]. Most experts recommend treatment duration of 14 days, but this recommendation needs further research. The antibiotic choice is usually empirical and based on the local microbial patterns and sensitivities. Before starting antibiotics, a sputum sample should be sent for culture and then empirical antibiotics should be started. In patients with unknown previous bacteriology, first-line treatment is amoxicillin 500 mg three times a day or alternatively clarithromycin 500 mg twice daily for 14 days is recommended. Higher doses of oral regimens may be needed in patients with severe bronchiectasis chronically colonised with H influenzae. Ciprofloxacin in doses 500-750mg twice daily should be used in patients colonised with P.aeruginosa[3]. Prulifloxacin is a new fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including P.aeruginosa[12]. It has been approved for exacerbations of COPD, but its therapeutic effect has not been studied in exacerbations of bronchiectasis yet[13]. More detailed information concerning antibiotic regimens for exacerbation of bronchiectasis can be found in the BTS guidelines, appendix 2, table AI[3]. Apart from exacerbations, studies have shown that bronchial colonization by pathogenic microorganisms and especially P.aeruginosa is an independent predictor of mortality, associated with more extensive disease, more frequent exacerbations, a longer duration of disease and worse pulmonary function status (Figure 2)[8,14,15]. Thus, following a failure of an initial attempt to eradicate using high doses of ciprofloxacin for

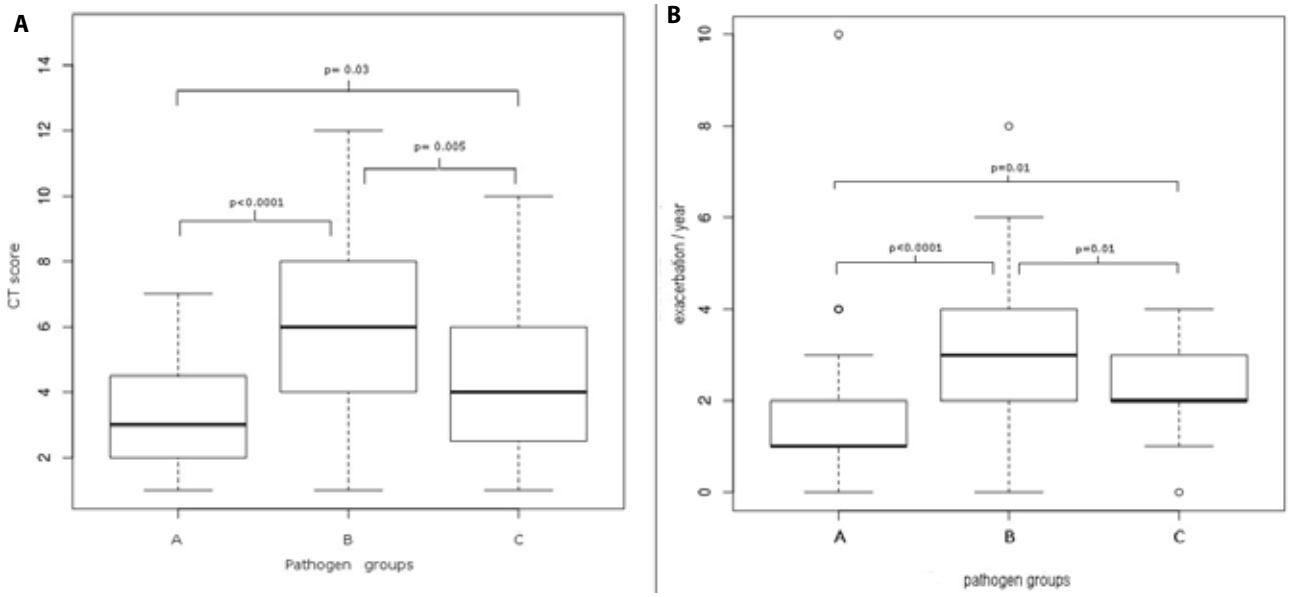

FIGURE 2. Bronchial colonization by pathogenic microorganisms and especially P.aeruginosa is associated with A, more extensive disease radiologically and B, more frequent exacerbations per year. Pathogen group A: no pathogen detected in sputum samples, group B: P.aeruginosa, group C: other pathogen (from reference 8).

14 days, certain eradication algorithms for P.aeruginosa have been established, through intravenous, oral or inhaled root of administration or in combination for an extended period of time (Figure 3)[3].

Long-term antibiotics

In recent years there has been enough evidence to support the use of long-term macrolides in non CF bronchiectasis. Azithromycin, erythrocin and clarithromycin are most commonly examined in clinical trials[16-20]. Along with their antibacterial effects, macrolides are well known to exert anti-inflammatory and immunomodulatory effects. Studies has shown a positive outcome regarding the annual number of exacerbation, which is a consistent finding, while improvements in dyspnea, sputum volume and quality of life measurements have also been reported. There is some concern about side effects and mainly cardiovascular events, hepatotoxicity, hearing loss and resistance in common bacteria and non tuberculosis mycobacteria (NTM) as well, so macrolides should be used with caution in some certain groups of patients. Patients should be examined with sputum culture for NTM before treatment initiation and with an ECG to detect prolong QT interval[3,6]. Treatment with long-term macrolides should be considered in patients with ≥3 exacerbations per year or those chronically colonized with P. aeruginosa or in patients with fewer exacerbations who present significant morbidity and impaired quality of life[3]. The optimal dose and duration of treatment remains to be defined. Azithromycin in the dose of 250-500mg three times per week for 3 to 6 months is the most commonly used regimen in clinical practice. There in not enough evidence for the long-term use of other categories of antibiotics in non CF bronchiectasis.

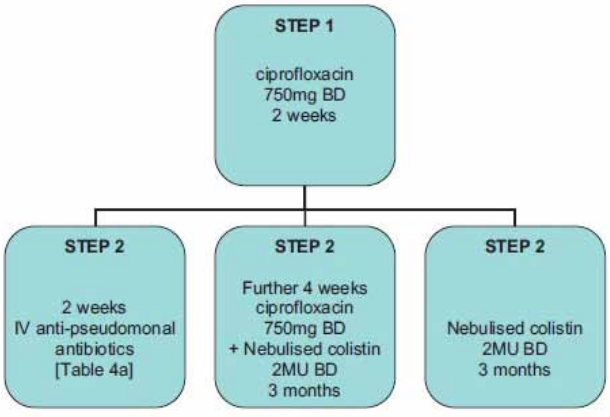

FIGURE 3. The eradication algorithm for P.aeruginosa as proposed by the British Thoracic Sosiety.

Inhaled antibiotics

Inhaled antibiotics have advantages over oral and intravenous administration by delivering higher concentrations of the drug to the bronchi and by reducing systemic absorption and therefore side effects[21]. Even though inhaled antibiotics in the management of patients with non CF bronchiectasis have gained a lot of attention in recent years, no officially approved treatment exists for the present. Several studies using different kind of inhaled antibiotics have reported positive effects in reducing sputum bacterial load, eradicating the bacteria from sputum, reducing the risk of acute exacerbations, reducing the sputum volume and purulence and improving symptoms and quality of life[22,23]. Therefore, clinical guidelines recommend the use of inhaled antibiotics in patients chronically colonized with P.aeruginosa and in patients who present 3 or more exacerbations per year or even in case of fewer exacerbations when they cause significant morbidity[3,9]. The choice of antibiotic should be guided by the antibiotic sensitivity results and by individual selection as tolerance issues are rather common and usually comprise of cough, bronchospasm, dyspnea and wheezing. Tobramycin and colistin are the most widely used antibiotics. A number of other inhaled antibiotics, such as gentamycin, amikacin, aztreonam and ciprofloxacin are being investigated in clinical trials in non CF bronchiectasis[21]. The dose and duration of treatment schedules are usually based on studies protocols or in severe cases on CF treatment protocols[21]. There are no data at the moment to support the use of inhaled antibiotics in the management of exacerbations of non CF bronchiectasis. The progressive development of new drug formulations and innovative nebulizers might increase effectiveness and tolerance by limiting their side effects in the near future.

Bronchodilators-inhaled corticosteroids

Despite the fact that inhaled bronchodilators, both β2-agonists and anticholinergic agents, are frequently prescribed in bronchiectasis, especially during exacerbations, the evidence for their regular use is rather weak[24,25]. However, there is a subset of patients with a significant bronchodilator response who should be recognized

through bronchodilator testing and may benefit from this kind of medication[26]. There is no evidence to support

the use of other bronchodilators such as methylxanthines in bronchiectasis[27]. Concerning inhaled corticosteroids, there are some data indicating a favorable response for bronchiectatic patients regarding reduced sputum volume and inflammatory markers in sputum and improved quality of life, without any effects in lung function or exacerbation parameters[28]. Patients with bronchiectasis and chronic airway limitation in lung function pattern may benefit from the combination of inhaled β2-agonists and corticosteroids[29]. Once again, current evidence does not support routine use of inhaled corticosteroids in bronchiectasis. The co-existence of bronchial asthma and COPD should be carefully examined in order to start or discontinue inhaled regimens. Moreover, adverse events with the use of inhaled corticosteroids such as the risk of pneumonia noted in COPD patients should be taken in account[30]. Finally, there is no evidence for oral corticosteroids in bronchiectasis[3,9].

Airway clearance

Even though the evidence for physiotherapy interventions in bronchiectasis is weak, airway clearance techniques and exercise should be recommended to all patients, especially for those who have chronic productive cough or evidence of mucus plugging and especially during exacerbations[6]. Airway clearance techniques have been found safe, while improvements in sputum expectoration, reduced hyperinflation and improved health-related quality of life have been also recorded[31]. There is a wide variety of manual or device mediated airway clearance techniques, that patients should be informed of in order to choose the most suitable and effectual for them with the guidance of a specialist respiratory physiotherapist. A variety of inhaled hyperosmolar agents and mucolytics have been used adjunct to physiotherapy to improve mucociliary clearance and help patients to clear their airway secretions[32]. Sputum yield, viscosity and ease of sputum expectoration are also improved by nebulized normal saline prior to physiotherapy, while hypertonic saline seems even more effective[14]. Pretreatment with a bronchodilator may be necessary for some patients to avoid bronchoconstriction. The use of inhaled dry power mannitol has been controversial. Studies have shown an increased sputum weight in favor of mannitol but this was not reflected to quality of life of exacerbation parameters[33,34]. As for mycolytics, there is little evidence

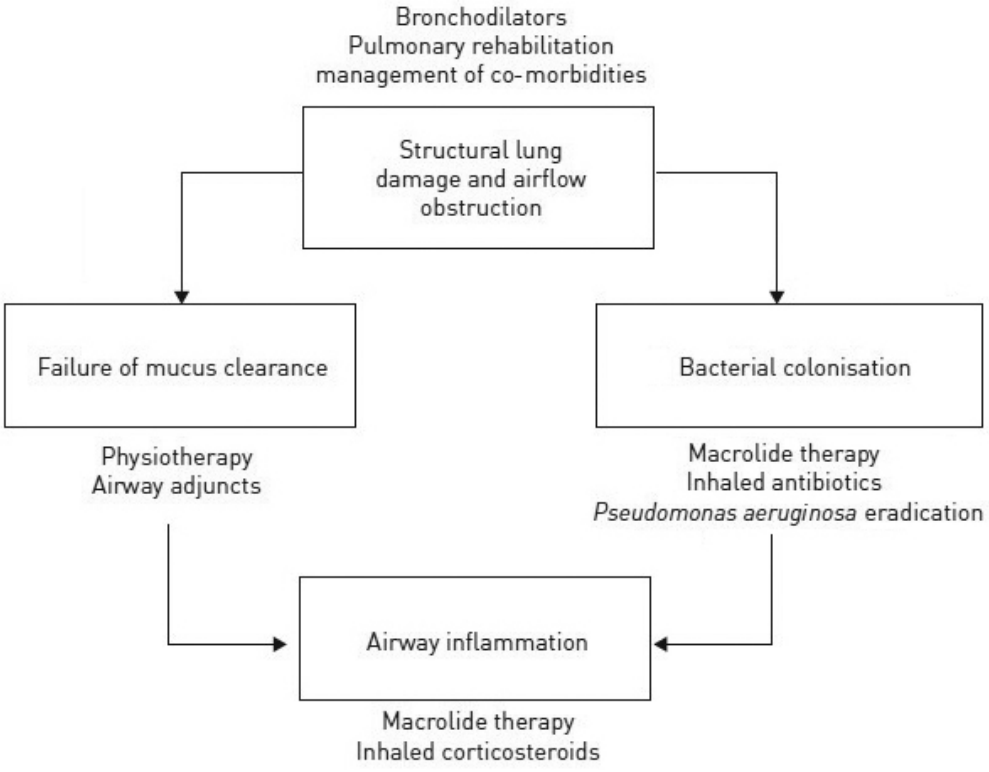

FIGURE 4. Current therapies for bronchiectasis according to the pathophysiology of the vicious cycle hypothesis (from reference 6).

to support the use of bromhexine in the treatment of bronchiectasis exacerbations[35]. In addition, recombinant DNase should not be used in patients with non CF bronchiectasis as it has been found to worsen lung function[36]. Finally, pulmonary rehabilitation has also been found helpful for bronchiectatic patients regarding exercise tolerance, improved dyspnea and quality of life and reduced exacerbations[37,38].

Current therapies for bronchiectasis according to the pathophysiology of the vicious cycle hypothesis are outlined in a comprehensive figure (Figure 4).

Interventional treatment

The management of major and life-threatening complications such as haemoptysis is crucial. Nowadays, there is enough experience, availability and evidence of success of bronchial artery embolization in severe or recurrent haemoptysis due to bronchiectasis[39-41]. Surgery is rarely employed in selected cases that severe or massive haemoptysis from a localized area of the lung with bronchiectasis is identified to be the cause of bleeding and embolization is not feasible[3]. In addition, in cases of highly localized bronchiectasis which cause symptoms that cannot be controlled by maximal medical therapy, minimal surgical interventions may be considered as well. Lung transplantation should be considered for end-stage disease, especially for those with FEV1 <30% or if there is a rapid progressive respiratory deterioration despite optimal medical management[3].

New therapies for bronchiectasis either with agents already available for treatment for other diseases such as roflumilast[42], or novel agents such as oral neutrophil elastase inhibitors targeting neutrophilic inflammation[43] are expected to be developed in the near future.

Significant advance has been made in the diagnosis and management of bronchiectasis in recent years. It is essential to separate bronchiectasis from the other classical obstructive pulmonary diseases and create a special, updated chapter in pulmonology regarding the appropriate management of non CF bronchiectasis. To achieve this goal, both basic research and more clinical trials are necessary in the future. New recommendations and guidelines from the ERS task force group are now under preparation.

COMPETING INTERESTS

The authors have indicated no financial conflicts of interest.

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