

Non-cystic fibrosis bronchiectasis in the elderly: current perspectives

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Abstract: Bronchiectasis is a chronic lung disease with permanently damaged airways predisposing to recurrent respiratory tract infections. There is an increasing prevalence of bronchiectasis in the elderly, affecting approximately 10 patients per 1,000 population. Studies have shown that older, frailer patients tend to have a more severe and symptomatic disease, with those aged 80 and above with worse quality of life, increased hospitalization and increased mortality. These patients will be encountered by clinicians working in all aspects of elderly care. This review covers the various investigations and aspects of treatment for bronchiectasis and how they may be utilized in a more older and generally frailer population.

Keywords: respiratory, geriatrics, microbiology

Introduction

Bronchiectasis is a chronic inflammatory lung disease. It is characterized by permanent dilatation of the bronchial tree which leads to chronic sputum production and impaired bacterial clearance. The affected parts of the lungs develop a vicious cycle of failed pathogen clearance leading to frequent infections, chronic inflammation and ongoing structural damage. The main symptoms are daily cough, daily sputum production and frequent respiratory infections.

The incidence of non-cystic fibrosis bronchiectasis is 2–5 patients per 1,000 population.¹ It is more common in the elderly and older, frailer patients tend to have a more severe and symptomatic disease. In one study of over 1,200 patients with bronchiectasis, 50% were over 65 years old and 19.1% were over 75 years.² Increasing age is recognized as an independent risk factor for bronchiectasis severity.^{3,4} Other markers of generalized frailty in the elderly population such as impaired forced expiratory volume in 1 second (FEV₁), low body mass index (BMI) and recent hospitalization also impact on the disease severity.³ It is recognized that existing comorbidities such as malignancy, cognitive impairment and ischemic heart disease affect the estimated 5-year mortality and the likelihood of hospitalization with a severe exacerbation.⁵

The etiology of non-CF bronchiectasis is multifactorial but the majority of cases are idiopathic or post infective.⁶ There is no current curative treatment for the majority of cases. Management is supportive and aimed at aiding sputum clearance, preventing further decline in lung function and reducing the frequency of infections. Various treatments may prove more difficult in the elderly due to comorbidities and side effects.

Diagnosis

Bronchiectasis should be suspected in patients who exhibit daily sputum production and suffer frequent chest infections. During infections sputum often increases in both

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volume and purulence.⁶ Generalized lethargy is common. Physical examination may reveal finger clubbing, coarse crackles in the affected lobe and there may be an expiratory wheeze, particularly during exacerbations. In advanced cases, there may be signs of cor pulmonale.

The persistent or recurrent growth of various organisms from sputum samples should raise the suspicion of bronchiectasis. In particular *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa* are common organisms seen in bronchiectasis.⁷ Repeated growth, particularly when the patient is not suffering from an exacerbation suggests bacterial colonization and this should prompt investigations for underlying bronchiectasis.

The gold standard test for diagnosis of bronchiectasis remains high resolution computed tomography (CT) scan of the chest. The diagnostic features include bronchial wall dilatation with or without thickening. The classical description is the Signet Ring sign where the internal diameter of the bronchial lumen is wider than the accompanying pulmonary vessel.⁶ CT scans can also suggest an underlying etiology for the bronchiectasis such as allergic bronchopulmonary aspergillosis (ABPA) or non-tuberculosis mycobacterium (NTM).

With increasing numbers of chest CT scans being performed we are discovering large numbers of seemingly incidental findings. In the elderly population there is a significant correlation between advancing age and CT changes such as sub-pleural bands, cysts and changes to bronchial wall thickness and dilatation.⁸ A study by Winter et al reviewed lung parenchymal findings on high resolution CT scans in asymptomatic non-smokers.⁹ The participants included 47 over-65-year-olds recruited from a geriatric outpatient clinic compared with 24 younger individuals. All volunteers had normal spirometry and echocardiogram findings. Subgroup analysis showed that in those aged 75 years and older there was a high incidence of radiological bronchiectasis (19.1% vs 0.0%). Similar studies have shown that the broncho-arterial ratio, a defining marker in the radiological diagnosis of bronchiectasis increases in older patients regardless of symptoms.¹⁰

Thus in the elderly, patients may have radiological bronchiectasis but should only be managed as having bronchiectasis if they fit the clinical syndrome of having regular cough with sputum production and recurrent respiratory tract infections.

Work up and investigations

Following the diagnosis of bronchiectasis on CT scanning there are various further investigations that should be performed.

Where patients are of an advanced age or frail then a decision should be made as to the appropriateness of these tests.

The British Thoracic Society (BTS) guidelines for bronchiectasis suggest all patients should undergo the following investigations:⁶

- Baseline spirometry and peak expiratory flow rate. Different patterns can be seen; normal, obstructive or restrictive patterns. Reversibility testing is recommended if there is an obstructive or restrictive deficit to look for reversibility.
- Sputum culture, both at times of exacerbations to identify causative organisms and when clinically well to identify colonizing bacteria. It is important to send a baseline culture for extended mycobacterium testing.
- Immunoglobulin levels. Both primary and secondary immunoglobulin deficiency (in particular IgG deficiency) can be associated with bronchiectasis and the frequency of infections can often be reduced by immunoglobulin replacement therapy. This treatment has been studied in elderly populations and seems well tolerated, although thoughts need to be given to the ability of the patient or carer to administer sub-cutaneous immunoglobulin therapy at home.¹¹
- All patients should undergo testing for ABPA. Diagnosis is dependent on radiological features (fleeting infiltrates are seen initially, it can eventually lead to proximal bronchiectasis) and tests to confirm aspergillus hypersensitivity (raised peripheral blood eosinophils, raised total IgE, positive skin test or raised aspergillus specific IgE with or without aspergillus precipitins). Patients with ABPA should be discussed with a local secondary care respiratory service. Treatment is often with prolonged courses of oral steroids with or without anti-fungal agents as steroid sparing agents.
- The possibility of co-existing inflammatory bowel disease, connective tissue disease or vasculitis should be considered. Co-morbidities are more likely in the elderly and clinical suspicion will warrant relevant screening such as ANCA, anti-CCP, fecal calprotectin etc. Bronchiectasis associated with connective disease such as rheumatoid arthritis is often more aggressive and carries a worse prognosis.¹²
- The possibility of cystic fibrosis should be considered in all adult patients diagnosed with bronchiectasis. Atypical CF can present in later life and may not involve all features of the disease such as gastro-intestinal symptoms or pancreatic insufficiency. This diagnosis becomes less likely in older patients although diagnosis in the sixth and seventh decade is documented.¹³ If a clinician suspects

that a patient may have CF underlying their bronchiectasis then referral to respiratory secondary care services should be made where sweat tests looking for increased chloride levels and genotyping for the most common mutations can be performed.

- Ciliary investigations to identify underlying primary ciliary dyskinesia (PCD) are rarely performed in the adult population and the condition is usually picked up in childhood, although there are rare cases documented in the seventh decade.^{14,15} Currently nasal nitric oxide is a good screening tool for the diagnosis of primary ciliary dyskinesia with low nasal nitric oxide levels (<77 nL/minute) being indicative of PCD.¹⁶

Etiology

The majority of bronchiectasis is either post infective or idiopathic. Table 1 represents a list of various causes. In a study of bronchiectasis etiology carried out by Lonni et al ciliary dysfunction, immunodeficiency, and inflammatory bowel disease (IBD) related were more common in younger patients. COPD-associated bronchiectasis was the most common cause in those aged above 75.¹⁷

Treatment

The treatment of bronchiectasis focuses on managing symptoms, slowing decline in lung function and preventing exacerbations. Patients should be encouraged to take general changes that will make a large difference such as smoking cessation. Chest physiotherapy is a well-established treatment with little in the way of side effects. Some patients may respond to more specialist treatments such as regular antibiotics, often in the form of a low dose macrolide three times a week. Frailty and co-morbidities play a role in deciding on the appropriateness of these treatments.

Treatment of exacerbations

The European Respiratory Society has defined bronchiectasis exacerbations as a deterioration in three or more of the following symptoms for at least 48 hours; cough, sputum

volume/consistency, sputum purulence, breathlessness/exercise tolerance, fatigue/malaise and hemoptysis.¹⁸ The majority of exacerbations of bronchiectasis are treated in the community with oral antibiotics. The British Thoracic Society recommends 14 days of therapy for all exacerbations, based on previous sputum microbiology when possible. A shorter course may be feasible in patients with mild bronchiectasis (7–10 days). If there is no known previous sputum microbiological results then initial treatment should be with amoxicillin or doxycycline/clarithromycin if penicillin allergic. For certain patients, admission to hospital is required, either for oxygen therapy due to hypoxia, or intravenous antibiotic therapy. This is laid out in the BTS guideline for bronchiectasis.⁶ General ability to cope in the community with an exacerbation is another obvious factor. Elderly patients are more likely to require admission during an exacerbation, simple exacerbations can be complicated by social isolation and lack of support or by acute delirium.¹⁹

Eradication

Bacterial colonization is a frequent occurrence in bronchiectasis and *P. aeruginosa* is a particularly common colonizing organism in more severe bronchiectasis. Patients with *P. aeruginosa* have a more rapid decline in their lung function and a worse prognosis. They experience more frequent exacerbations and hospitalization.²⁰ It may be appropriate to attempt eradication with an anti-pseudomonal antimicrobial agent such as ciprofloxacin or piperacillin-tazobactam, particularly for those patients with deteriorating lung health. Age is significantly associated with *Clostridium difficile* infection secondary to antimicrobial use. Consideration of the side effects of all antimicrobial agents should be taken when dealing with a more elderly and frail population.²¹

Chest physiotherapy and pulmonary rehabilitation

A central component in the management of bronchiectasis is to educate patients to perform daily sputum clearance techniques. This empowers patients suffering from bronchiectasis to improve quality of life, manage symptoms as well as removing harmful organisms and inflammatory cells from their airways. Various techniques exist,²² but the Active Cycle of Breathing Technique is the most frequent technique performed in the UK. All patients should see a respiratory physiotherapist to find a technique that suits them to aid compliance. A randomized crossover trial of patients comparing twice daily chest physiotherapy augmented with

Table 1 List of the most common causes of non-CF bronchiectasis

Causes of non-CF bronchiectasis	
Idiopathic	Post-infective (ie, tuberculosis, pertussis)
ABPA	Chronic aspiration/GORD
Immunoglobulin deficiency	Ciliary dysfunction
Connective tissue disease related	Rheumatoid arthritis-related
Airways disease (asthma/COPD)	Non-tuberculosis mycobacterium
Foreign body inhalation	Inflammatory bowel disease-related

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; GORD, gastroesophageal reflux disease.

a positive pressure oscillating device vs no physiotherapy found significant improvements in quality of life, 24-hour sputum expectoration and exercise tolerance.²³

On review of the literature there appears to be little published evidence on the positives and potential limitations of these interventions in the elderly population. It is predictable that both physical and cognitive impairments will limit the ability to perform satisfactory chest physiotherapy, although this is an area that requires further research. A pragmatic approach to physiotherapy in the elderly, frail patient will be necessary.

Various pharmacological adjuvants can be used to aid chest physiotherapy in the treatment of sputum retention. Inhaled bronchodilators such as salbutamol are useful in those with bronchial hyperreactivity. Many patients find benefit in nebulized isotonic (0.9%) and hypertonic saline (3%–7%). Their mode of action is in reducing sputum viscosity and aiding clearance. Small studies have shown to date that hypertonic saline has similar efficacy to isotonic saline at improving ease of expectoration and has a modest benefit on lung function.²⁴ Larger studies are needed. Bronchospasm is a potential side effect and the use of concomitant nebulized bronchodilators may be necessary.

Studies of nebulized mannitol failed to reach the primary end point of reduced exacerbations and so it is unlikely to be licensed for use in bronchiectasis.²⁵ Nebulized recombinant human DNase has been used with considerable success in the cystic fibrosis community but its use in non-CF bronchiectasis is not recommended because its use is associated with increased exacerbations and loss of lung function.²⁶

In addition to specialized chest physiotherapy techniques there is a range of various positive expiratory pressure (PEP) devices available which can assist with sputum clearance and respiratory function.²⁷ Options include devices such as flutter device and acapella. The exact mechanism behind each machine is different but generally they produce oscillating end expiratory pressure which vibrates the airways and loosens sputum to aid expectoration. Many PEP devices are handheld and their use can reduce the time and effort required for chest physiotherapy.²⁷

Pulmonary rehabilitation programs are a well-established intervention in patients suffering from COPD.²⁸ The focus is on managing dyspnea, improving exercise tolerance and helping patients live their life in spite of their condition. The course often takes place over 6 weeks and is a program of exercise, education, and support to help patients maximize their potential. Medical aspects of the patient's condition such as inhaler therapy are covered, as well as general advice

on health such as diet, nutrition, and exercise. Pulmonary rehabilitation is often used for breathless patients with bronchiectasis if their breathlessness affects their activities of daily living.²⁹

Vaccination

Patients with chronic respiratory illnesses are advised to get the pneumococcal vaccination, as well as annual influenza vaccination. In a 2-year retrospective cohort study of over 1,800 patients Nichol et al have shown that a one off pneumococcal vaccination in patients aged 65 years and older who suffer from a chronic lung condition is associated with fewer hospitalizations and a lower mortality.³⁰

Meta-analysis has shown that annual influenza vaccination in the general elderly population reduces the risk of pneumonia, hospitalization, and death.³¹

The BTS bronchiectasis guidelines recommend that patients with non-CF bronchiectasis receive a one-off pneumococcal vaccination and annual influenza vaccinations.⁶

Inhaled therapy

Inhaled corticosteroids are recommended to be used in the treatment of bronchiectasis where there is co-existing obstructive airways disease such as asthma, COPD or ABPA.⁶ Spirometry and reversibility studies can help select appropriate patients. There is evidence that shows that inhaled drug delivery in the elderly can be inadequate.³² The main barriers to effective inhaler technique in the elderly includes poor vision, lack of manual dexterity, and cognitive impairment. It is important that regular inhaler technique checks are carried out in all patients and especially those of an advanced age.³³

The BTS bronchiectasis guidelines recommend a trial of bronchodilator therapy if shortness of breath affects the patient's activities of daily living.⁶ 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.

Long-term antibiotic therapy

Long-term oral antibiotics are recommended for patients if they have suffered three or more exacerbations in a 12-month period despite performing regular chest clearance and receiving appropriate vaccinations.⁶

Macrolides, such as azithromycin and clarithromycin are commonly used for not only their antimicrobial properties, but also their anti-inflammatory and immunomodulatory

properties. Much of the damage that takes place within the bronchi of patients with bronchiectasis is not necessarily caused by direct bacterial damage but due to the vicious cycle of infection and neutrophilic airways inflammation. Macrolide therapy may be useful for both its antimicrobial activities but also its anti-inflammatory properties.^{34–36}

Macrolide therapy carries the risk of various side effects and in general initiation and monitoring should be performed in specialist, secondary care units. Potential antibiotic resistance is a concern, as well as the potential risk of cardiotoxicity and ototoxicity. All these risks are heightened in an older age group with increased comorbidities, although in general there is a lack of published evidence. A review article of long-term macrolide therapy published in *Chest* describes the benefits and side effects of the treatment.³⁷ Macrolide therapy reduces the risk of exacerbation and slows the decline in forced expiratory volume in 1 second (FEV₁). Further studies are needed to assess the overall impact on quality of life. Adverse effects such as diarrhea are noted to be more common in the treatment arms of the various studies although there is not noted to be a difference in patient withdrawal in a general population. Long-term macrolide therapy has been shown to increase in vitro resistance in oropharyngeal flora. The long-term impact of this is not clear, but studies up to 1 year do not show any deleterious effect. QT prolongation and arrhythmia are rare but potentially significant side effects. The risk of arrhythmia is higher amongst patients with poor drug clearance or underlying cardiac disease³⁸ and it is important that patients are screened appropriately. An electrocardiogram should be performed in all patients prior to starting macrolide therapy and a corrected QT interval of >450 msec should prompt caution or exclusion.³⁷ It is important that simultaneous medications that prolong the QT interval are stopped – this is an important issue in the elderly patient cohort where polypharmacy is common. With the correct precautions however macrolide therapy can be a safe and effective therapy for elderly patients with bronchiectasis. A retrospective cohort study by Trac et al compared over 1 million older adult patients in Canada who had either received a macrolide or a non-macrolide antibiotic.³⁹ Their study found no statistical difference in the rate of ventricular arrhythmia or death at 30 days. It is important to note these patients had been given a short course as opposed to long-term therapy.

In addition to the possible cardiotoxic side effects of macrolides clinicians prescribing for elderly patients must also consider the potential for ototoxicity. In one randomized trial in the use of azithromycin for COPD there was a 25%

audiogram-confirmed decrement in the treatment group vs 20% in the control ($P=0.004$).⁴⁰ This hearing loss is generally reversible on cessation of the drug. Hearing loss in the elderly has the possibility to impact upon social inclusion and cognitive function.

It is good practice to perform an electrocardiogram and a clinical assessment of liver function and auditory function (if hearing or balance issues) prior to starting a long-term macrolide in the elderly. Patients should be advised if they develop any hearing or balance issues whilst on long-term macrolide therapy to seek urgent medical attention.

Macrolide therapy can be a problem if the patient subsequently develops non-tuberculosis mycobacterium disease as macrolides are employed in the multi-drug treatment of NTM, and thus resistance is a potential concern.⁴¹ NTM infection should be explored before macrolides are started. Ideally there should be at least one negative sputum mycobacterial culture.

Inhaled antibiotic therapy is an option in severe bronchiectasis, and carries less systemic side effect risk than oral agents. One small study by Tabernero et al found that inhaled colistin in the elderly was associated with a significant reduction in *P. aeruginosa* colonization although their study did not show any functional or clinical benefits.⁴² Thirty-one percent of patients in the treatment arm had to stop therapy due to adverse effects. Haworth et al found nebulized colistin at a dose of 1 million international units BD for 6 months prolonged the time to first exacerbation in those that complied with treatment (80% doses or more).⁴³ Murray et al found nebulized gentamicin 80 mg BD for 1 year reduced exacerbations and prolonged time to first exacerbation.⁴⁴ The studies of inhaled ciprofloxacin at 32.5 mg BD over 1 year are conflicting (one study showing reduced exacerbations and the other study showing no significant differences).^{45,46}

Long-term inhaled antibiotics are a means of reducing bacterial colonization and the frequency of exacerbations. Long-term inhaled antibiotics should be considered in those with frequent exacerbations (three or more per year) despite treatment with vaccination, physiotherapy and prompt treatment of exacerbations. The theory behind all inhaled therapy is to deliver a large concentration of medication to the desired area and bypass unwanted systemic side effects. Meta-analysis has proven inhaled antibiotic therapy to be effective and safe in reducing bacterial load, colonization and the risk of exacerbation.⁴⁷ Various anti-microbial agents are used including gentamicin, colomycin, amikacin, and aztreonam. Delivery is through a nebulizer. Systemic side effects are rare, although bronchospasm can occur in up to

10% of patients. This can often be managed with concurrent use of nebulized beta agonists. There are obvious benefits to using inhaled antibiotic treatment in the elderly where it is desirable to avoid systemic side effects. All inhaled antibiotic treatments are unlicensed in bronchiectasis. In the UK, nebulized gentamicin and colomycin are the most frequently used. Clinicians should avoid use of these agents in patients with balance issues or significant renal failure.

Non-tuberculosis mycobacterium

International studies show NTM can affect approximately 9% of patients with bronchiectasis.⁴⁸ These slow-growing organisms are difficult to diagnosis and can lead to both radiological and clinical decline. Diagnosis should be made after positive culture from two separate spontaneous sputum samples or one bronchoscopic washing sample. NTM disease should be considered where CT imaging shows fibro-cavitary disease or pulmonary nodularity with bronchiectasis. Older patients are more susceptible to NTM infection and are less likely to tolerate the 24 months of triple antibiotic therapy that is often required for eradication.⁴⁹ Drug toxicity is high⁵⁰ and should be initiated in secondary care if there is an agreement that clinical improvement is likely with the multidrug regime.

Surgery

A Cochrane review of surgical vs non-surgical management of non-CF bronchiectasis in 2000 found that the literature only included case series and that it was not possible to provide an estimate of the benefits of either approach.⁵¹ Surgical treatments for bronchiectasis include resection of limited areas of disease and lung transplantation. They are uncommon treatments in the general disease population and particularly so in an older cohort. In the author's opinion surgical resection may be indicated in episodes of major hemoptysis or limited areas of disease not controlled by medical therapy.

Lung transplantation is generally limited to patients under 65 years of age, although in very select groups it has been performed in the seventh decade.⁵²

Prognosis

Bronchiectasis is generally a progressive condition, but it can be difficult to predict long-term outcomes. There are currently two scoring systems for predicting mortality in bronchiectasis; the Bronchiectasis Severity Index (BSI) and the FACED score.^{3,4} Both systems are validated to predict future mortality rates, and the BSI also predicts future risk of hospitalization for 1 and 4 years. Both scoring systems include increasing age as an independent risk factor for

future deterioration. Data from the BSI suggests that those aged 80 and above have increased risk of hospitalization and 4-year mortality.⁴

The authors behind the BSI have produced a second scoring system, the Bronchiectasis Etiology and Co-morbidities Index which identifies that patients suffering from co-existing conditions such as ischemic heart disease, cognitive impairment, and diabetes have a worse outcome.⁵ This scoring system does not include age but we recognize that an older and frailer patient group often have multiple comorbidities which will impact on outcomes.

Bellelli et al have produced an analysis of six European databases of bronchiectasis patients looking specifically at the clinical characteristics of the older patients.² Their study included over 1,200 patients. They found that those patients of 65 years and older were more likely to be symptomatic of their condition, with a worse quality of life. Comorbidities were more common, and the older patients were more likely to die of the condition.

End-of-life planning

It is important to recognize the need for appropriate end-of-life and palliative care in patients with severe bronchiectasis. This can occur alongside the provision of active therapies such as antibiotics. Despite severity scoring systems it can be difficult when patients are entering the last months of their life, but there is an acceptance within the care of the elderly community of the importance of identifying patients at the end of life. Physical symptoms such as dyspnea, cough, phlegm, and hemoptysis need to be managed alongside spiritual and psychological concerns.⁵³ Appropriate discussions with patients and relatives should be had to decide on limitations of treatment, escalation decisions, and resuscitation.

Areas for further research

Research is needed to focus on investigations, diagnosis and management of non-CF bronchiectasis in the elderly cohort. This is increasingly relevant in view of the increasing comorbid and aging population. Tolerability of medical therapy and the potential for drug interactions affects treatment choice in this cohort and randomized control trials that focus on the elderly population are needed.

Conclusion

Non cystic fibrosis bronchiectasis is a chronic, inflammatory lung disease that is characterized by 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. Over half of patients with bronchiectasis are over 65 years old and the condition tends to be more severe in the elderly.

Many clinicians caring for elderly patients will encounter those suffering from bronchiectasis. The role for appropriate short- and long-term antimicrobial therapy and chest clearance techniques cannot be overstated.

Bronchiectasis can be progressive, and in such patients advanced care planning and palliative care have important roles.

Disclosure

The authors report no conflicts of interest in this work.

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